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(54) **EXTENDED RELEASE PHARMACEUTICAL FORMULATION**

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CPC ***A61K 9/28*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/2031*** (2013.01); ***A61K 9/2813*** (2013.01); ***A61K 9/2853*** (2013.01); ***A61K 9/2866*** (2013.01); ***A61K 31/135*** (2013.01); ***A61K 45/06*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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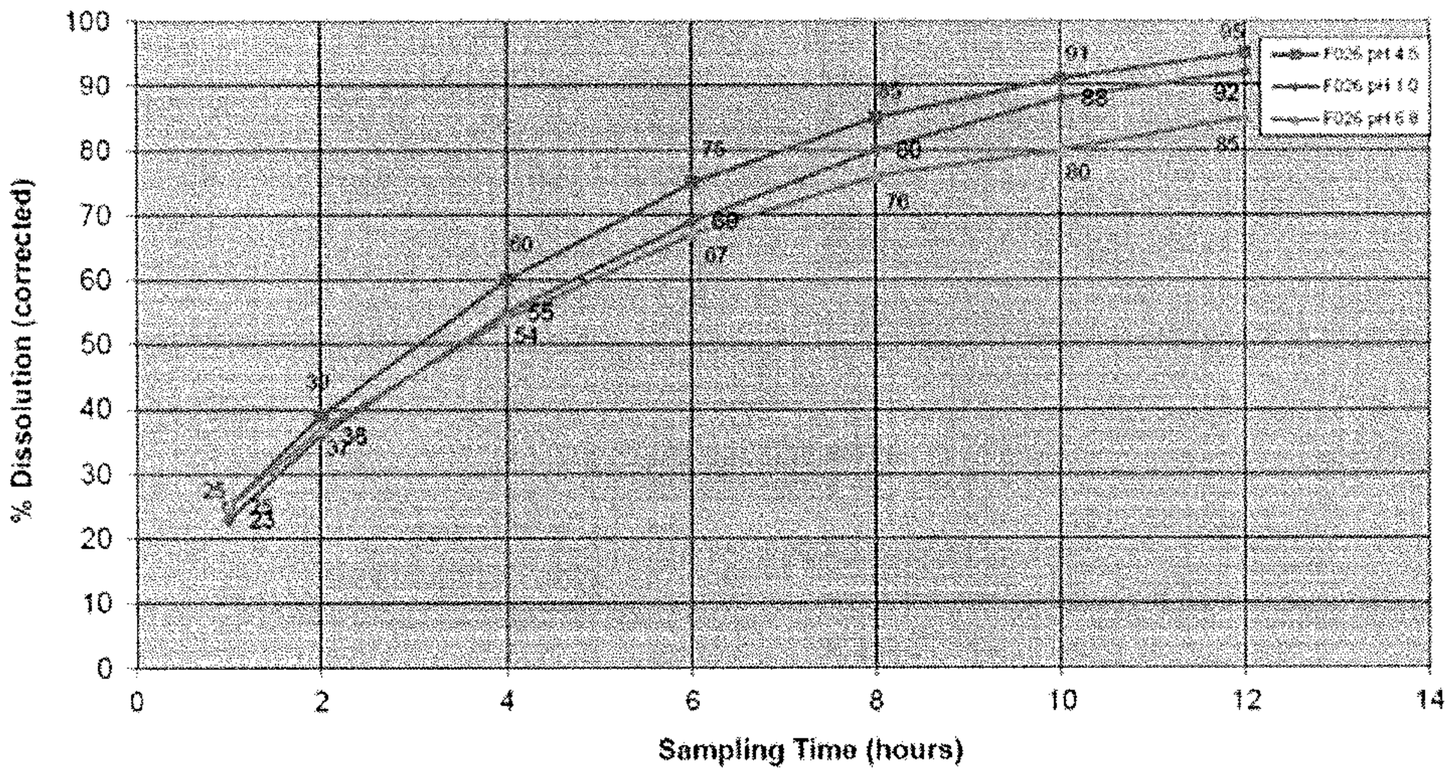
(57) **ABSTRACT**

The invention provides an oral extended release formulation for the treatment of treatment-resistant depression and treatment-resistant anxiety.

11 Claims, 12 Drawing Sheets



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* cited by examiner

Figure 1

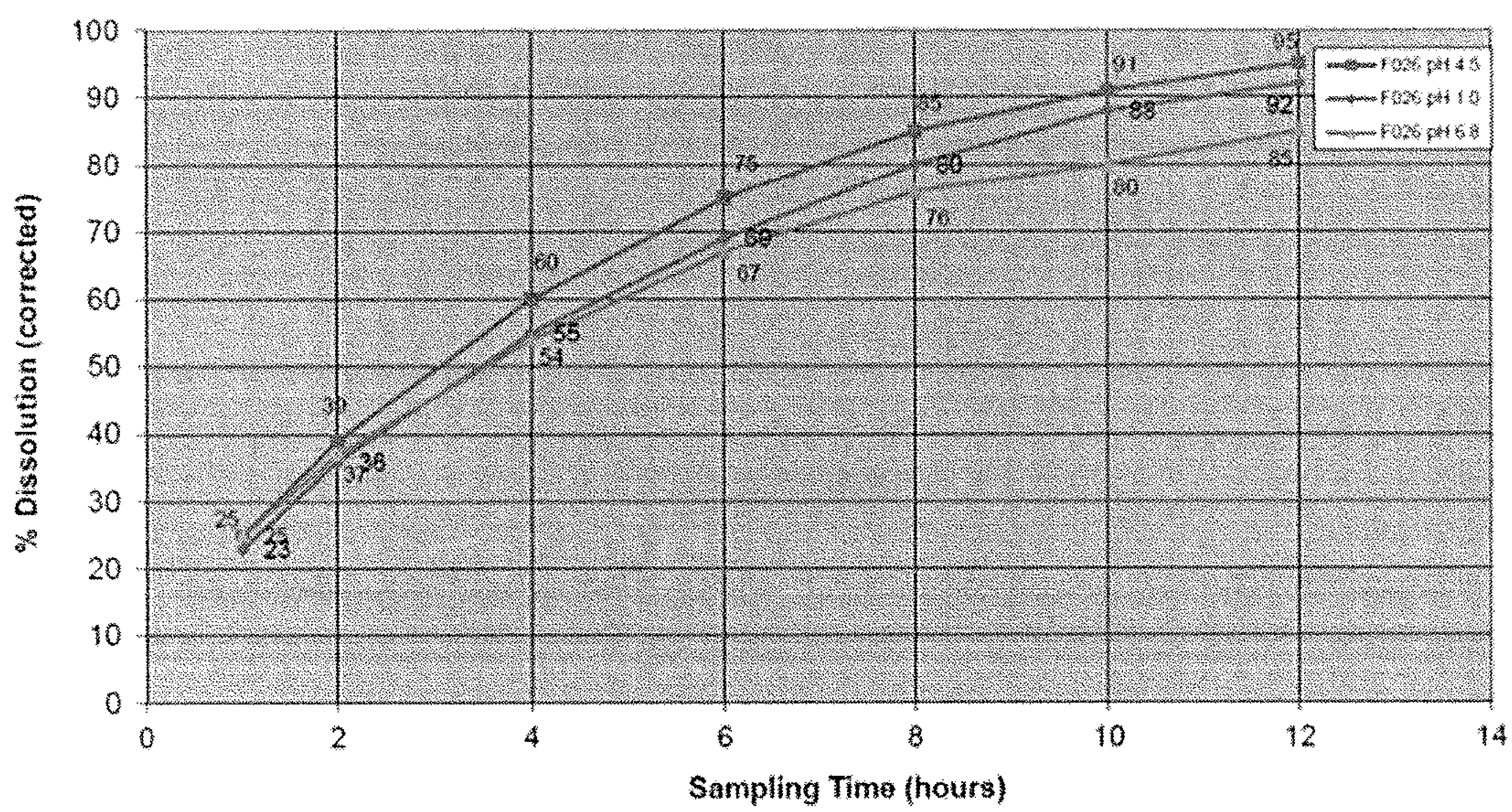

% Dissolution (corrected)
Sampling Time (hours)
F026 pH 4.5
F026 pH 1.0
F026 pH 6.8

Figure 2A

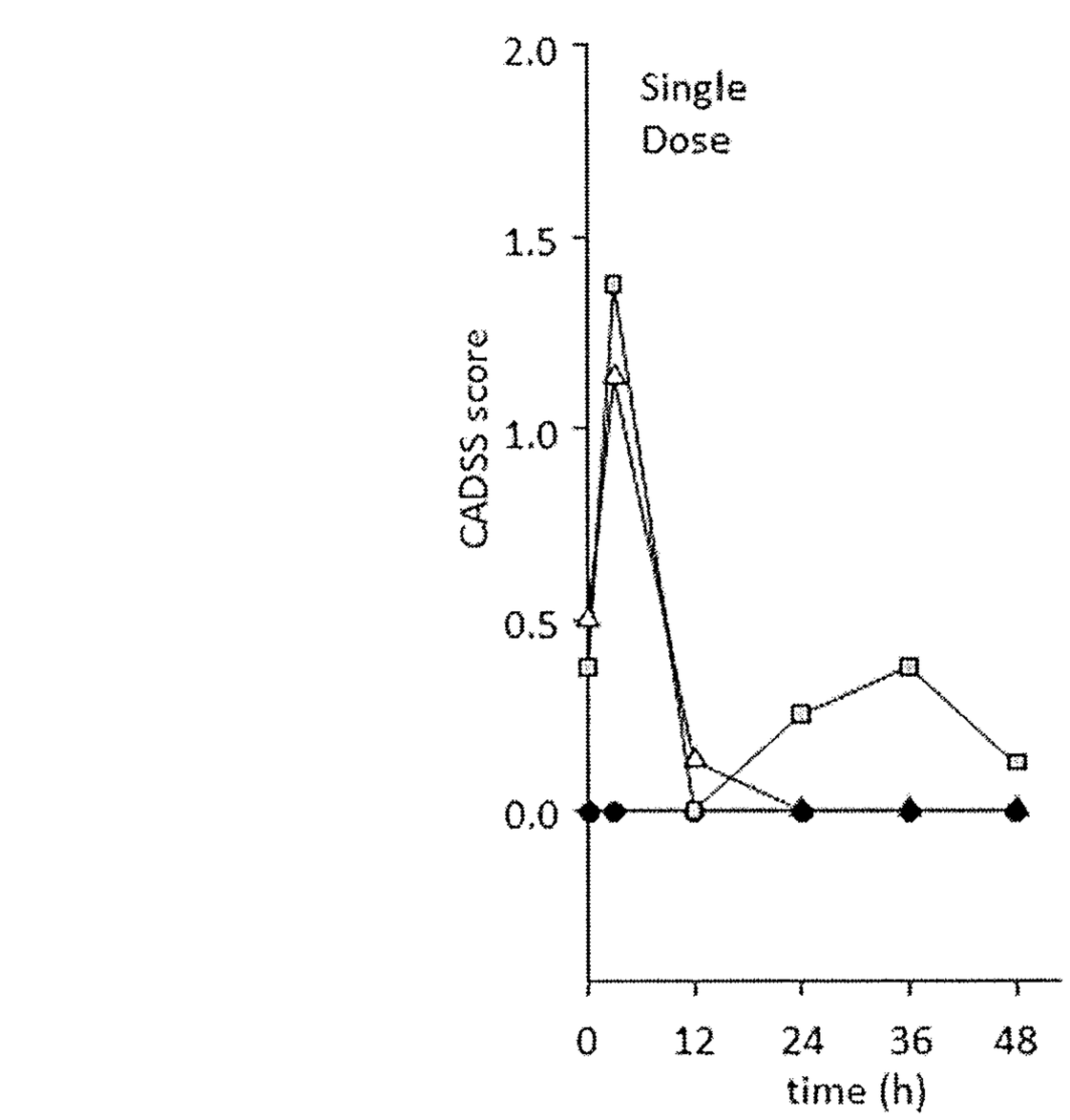


Figure 2B

Figure 3A

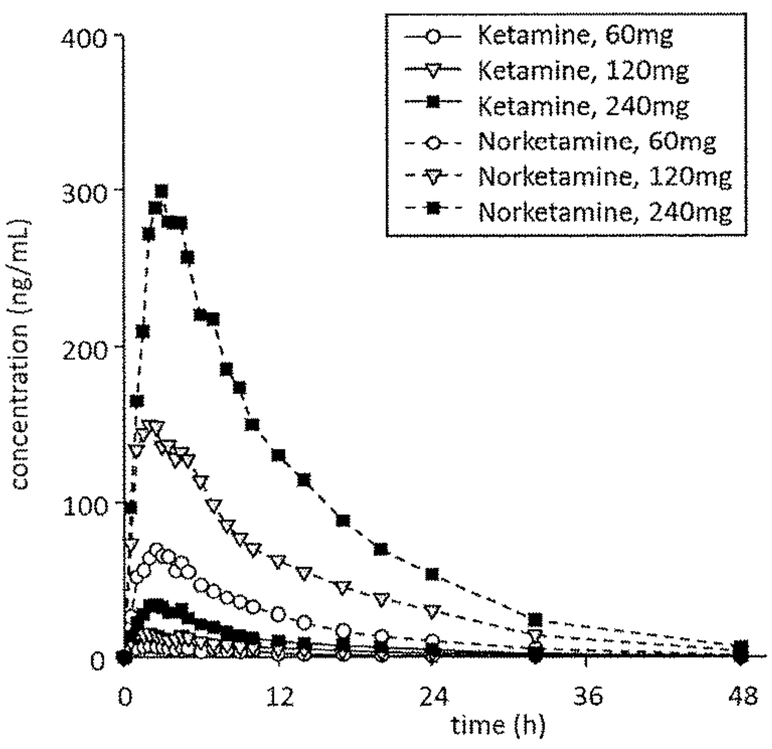
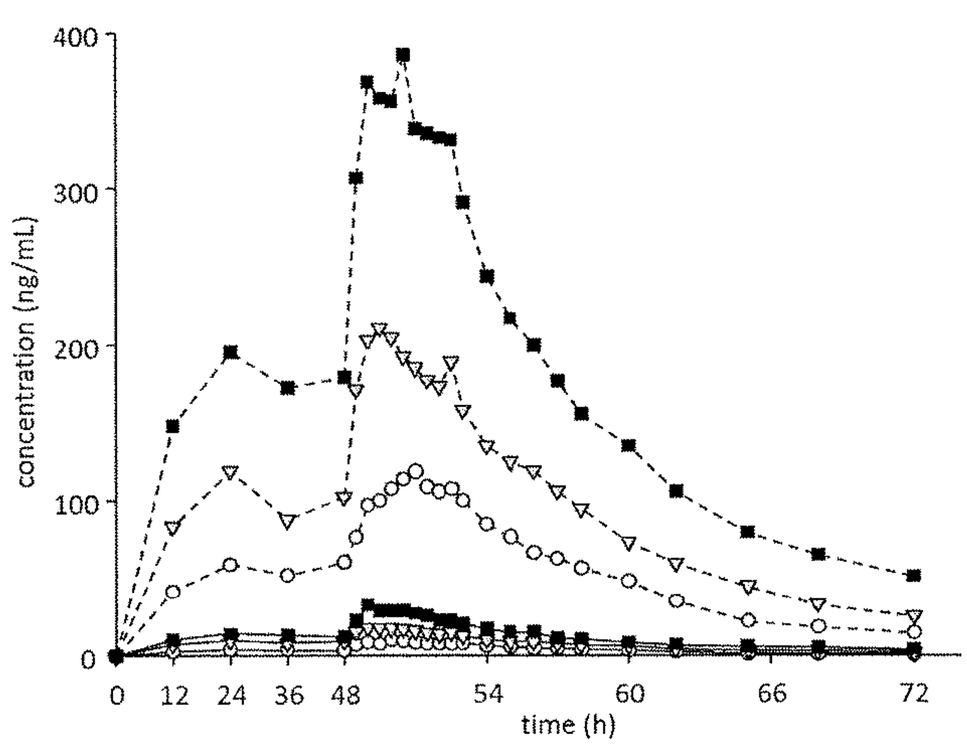


Figure 3B



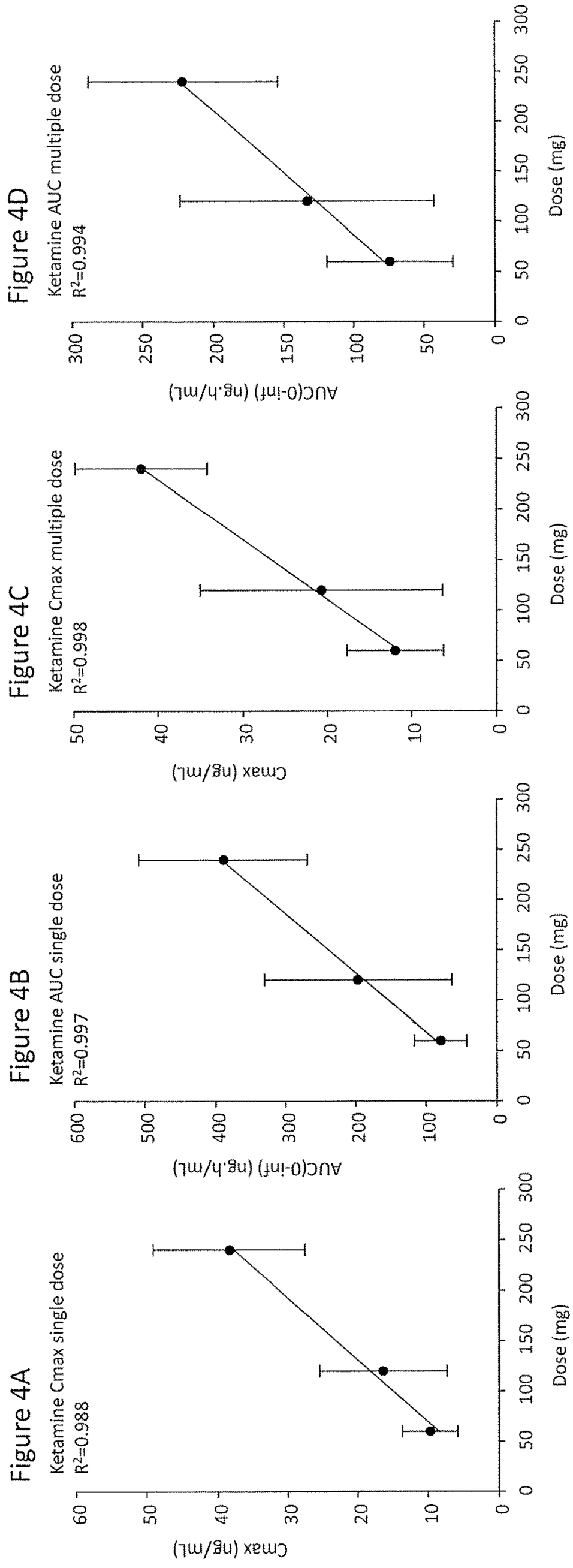


Figure 4D
Ketamine AUC multiple dose
R^2=0.994
AUC(0-inf) (ng.h/mL)
300
250
200
150
100
50
0
0 50 100 150 200 250 300
Dose (mg)
Figure 4C
Ketamine Cmax multiple dose
R^2=0.998
Cmax (ng/mL)
50
40
30
20
10
0
0 50 100 150 200 250 300
Dose (mg)
Figure 4B
Ketamine AUC single dose
R^2=0.997
AUC(0-inf) (ng.h/mL)
600
500
400
300
200
100
0
0 50 100 150 200 250 300
Dose (mg)
Figure 4A
Ketamine Cmax single dose
R^2=0.988
Cmax (ng/mL)
60
50
40
30
20
10
0
0 50 100 150 200 250 300
Dose (mg)

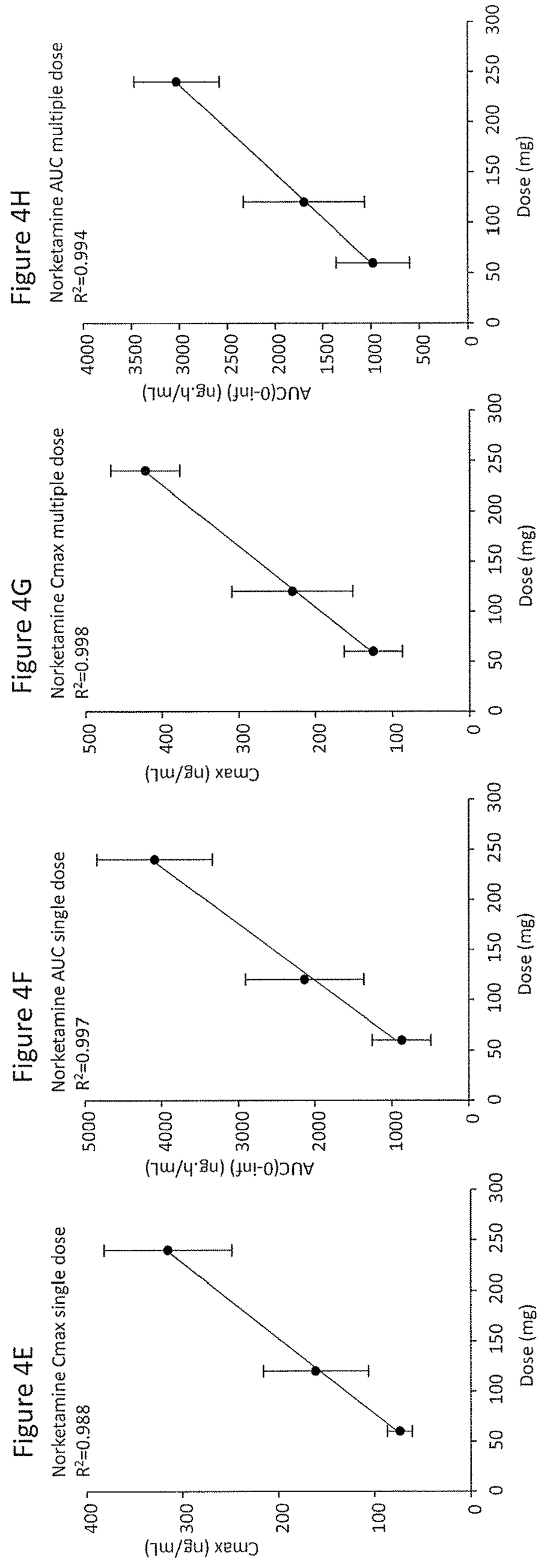


Figure 4H
Norketamine AUC multiple dose
R2=0.994
AUC(0-inf) (ng.h/mL)
4000
3500
3000
2500
2000
1500
1000
500
0
0
50
100
150
200
250
300
Dose (mg)
Figure 4G
Norketamine Cmax multiple dose
R2=0.998
Cmax (ng/mL)
500
400
300
200
100
0
0
50
100
150
200
250
300
Dose (mg)
Figure 4F
Norketamine AUC single dose
R2=0.997
AUC(0-inf) (ng.h/mL)
5000
4000
3000
2000
1000
0
0
50
100
150
200
250
300
Dose (mg)
Figure 4E
Norketamine Cmax single dose
R2=0.988
Cmax (ng/mL)
400
300
200
100
0
0
50
100
150
200
250
300
Dose (mg)

Figure 5A

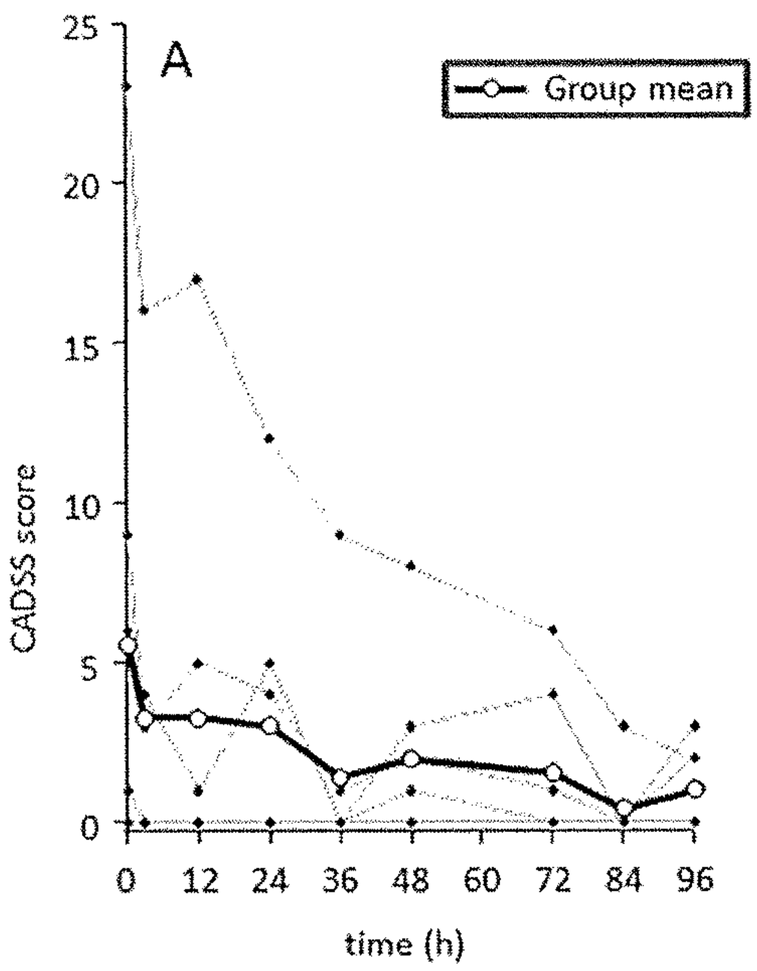


Figure 5B

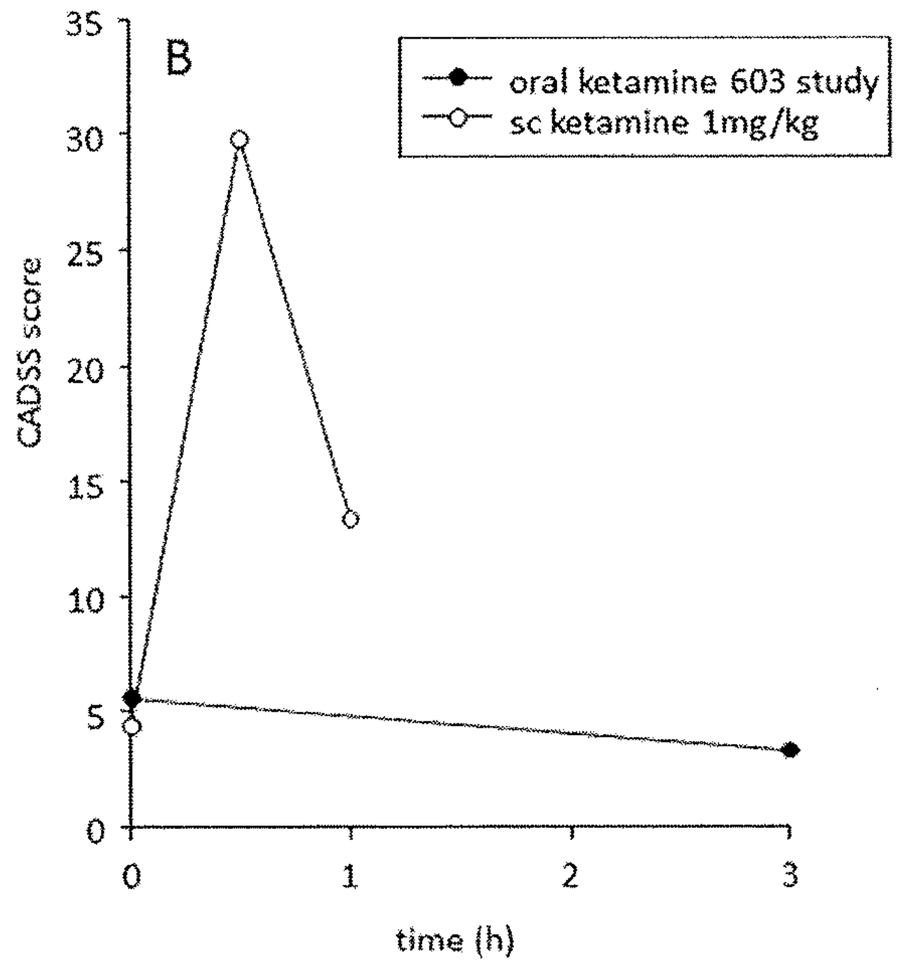


Figure 6A

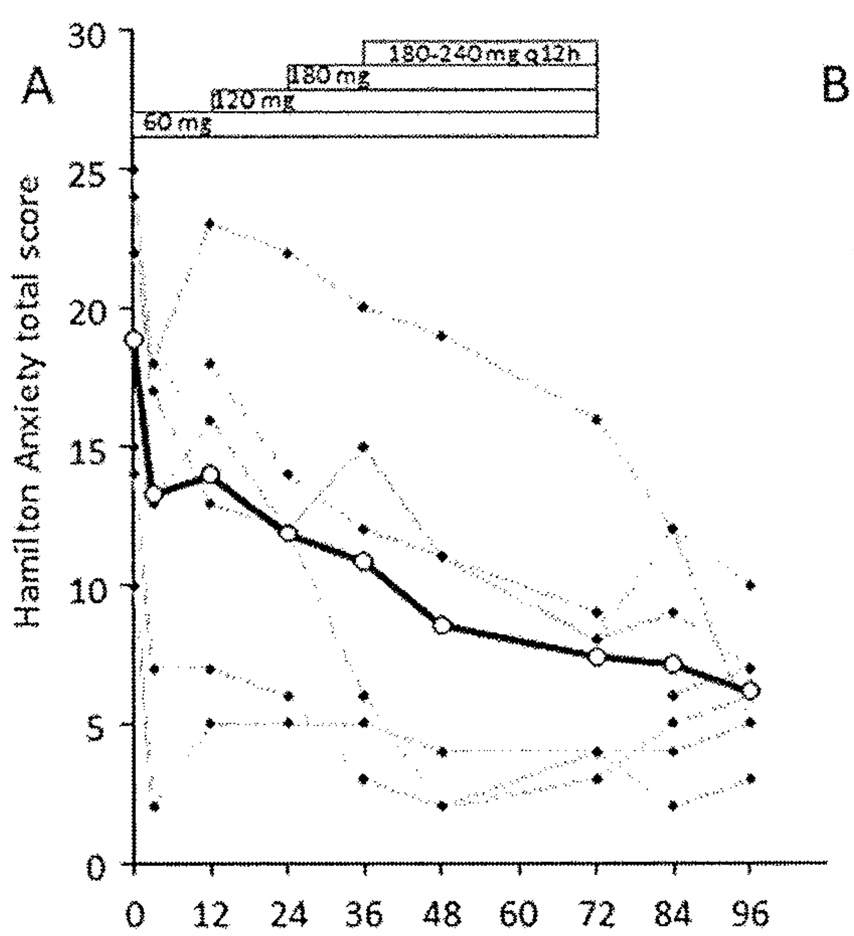
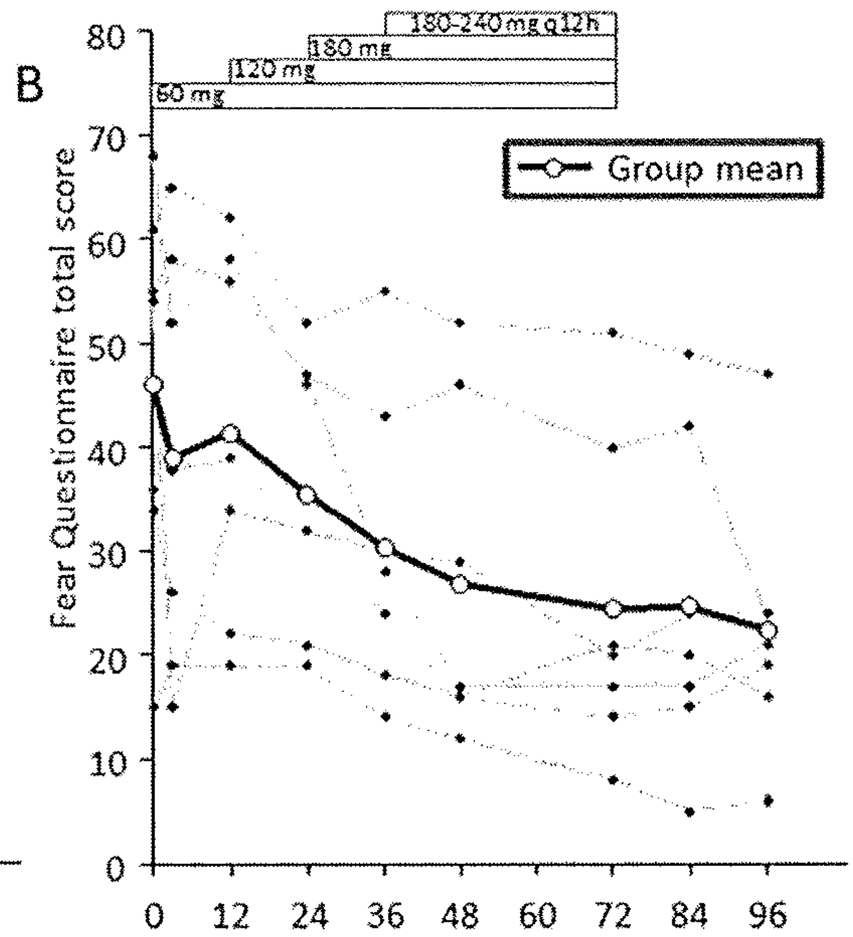


Figure 6B



Responders (>50% decline from baseline) 7/7

Figure 7

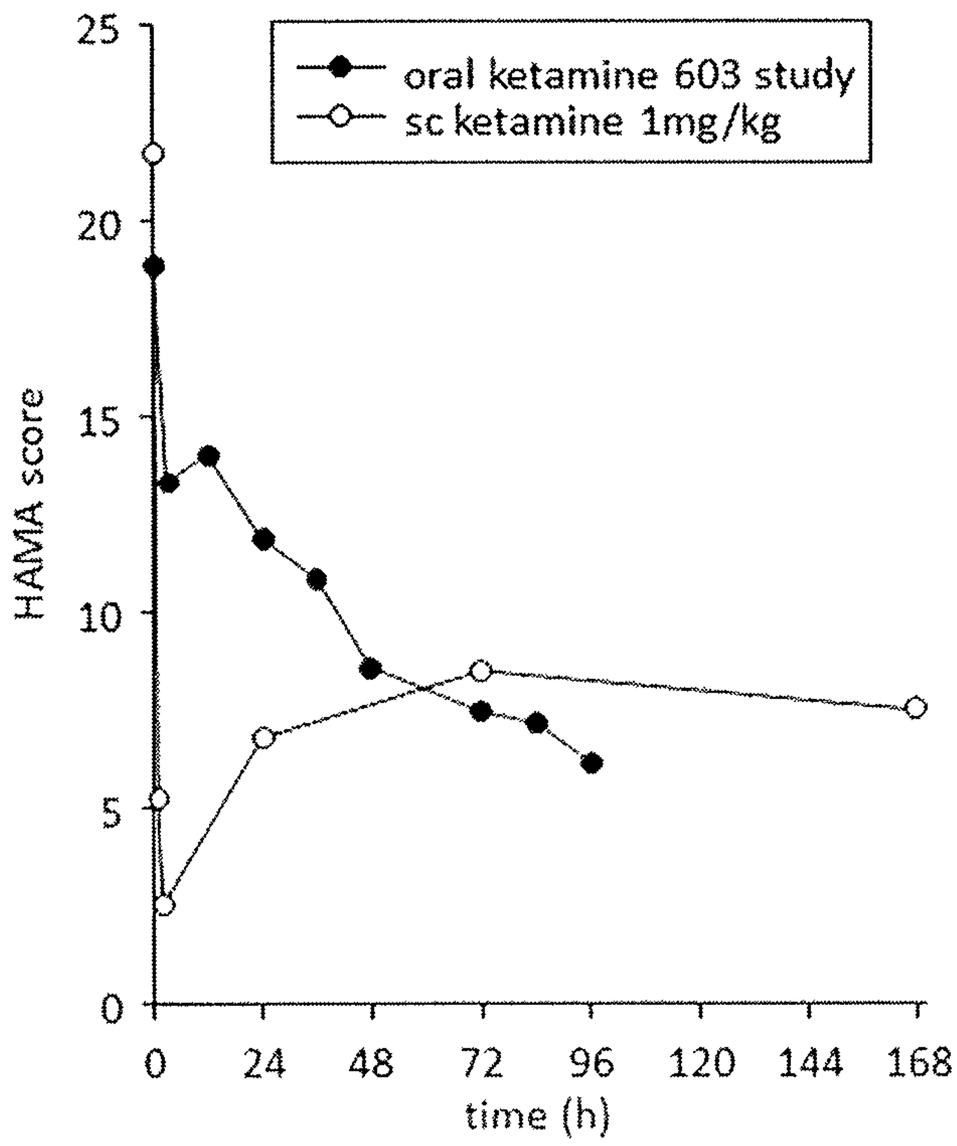
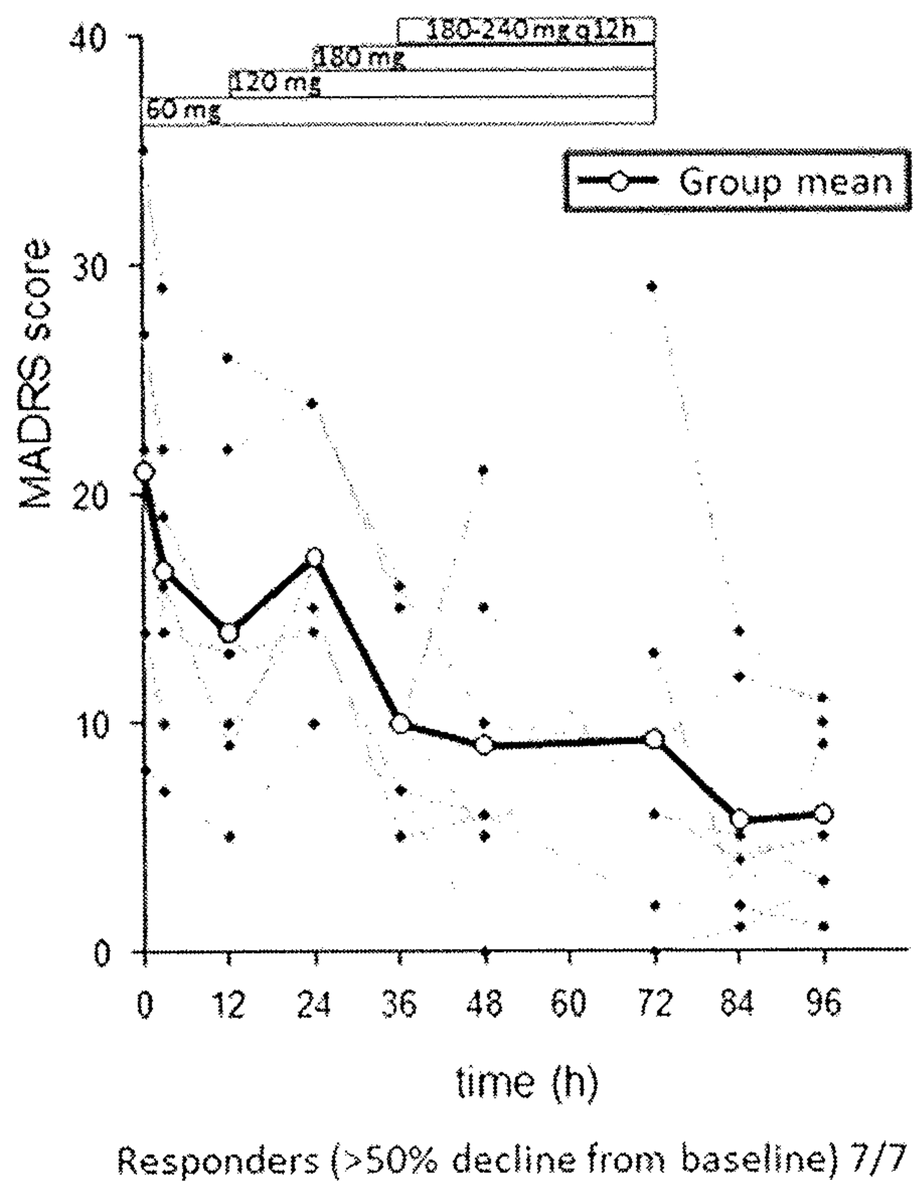

oral ketamine 603 study
sc ketamine 1mg/kg
HAMA score
25
20
15
10
5
0
0
24
48
72
96
120
144
168
time (h)

Figure 8



Responders (>50% decline from baseline) 7/7

Figure 9A

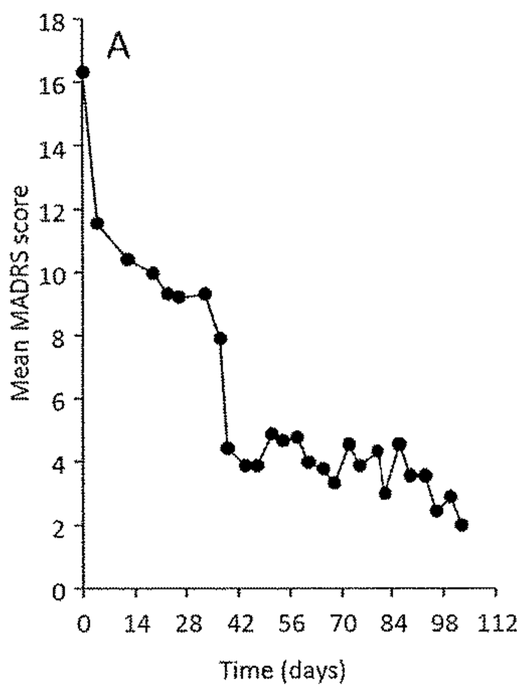


Figure 9B

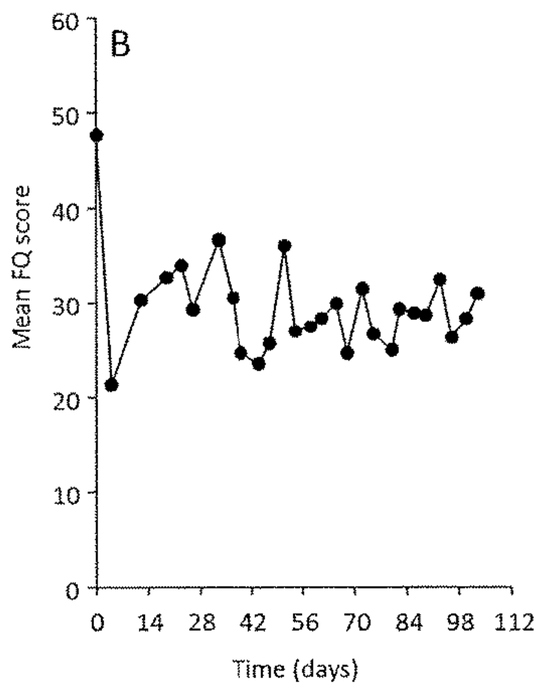


Figure 9C

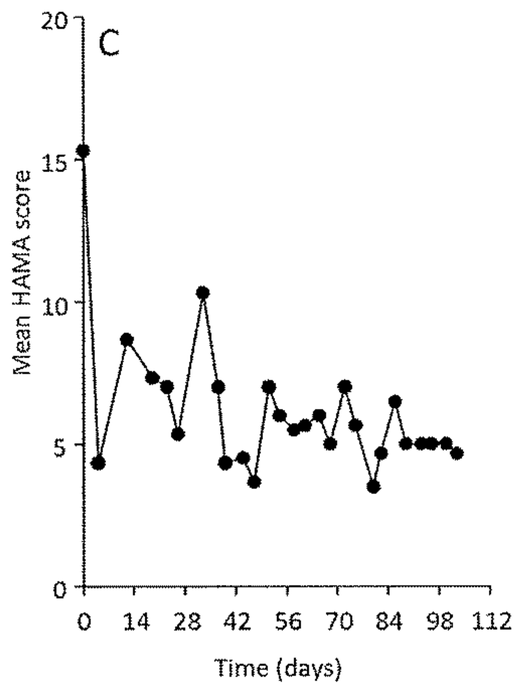


Figure 10

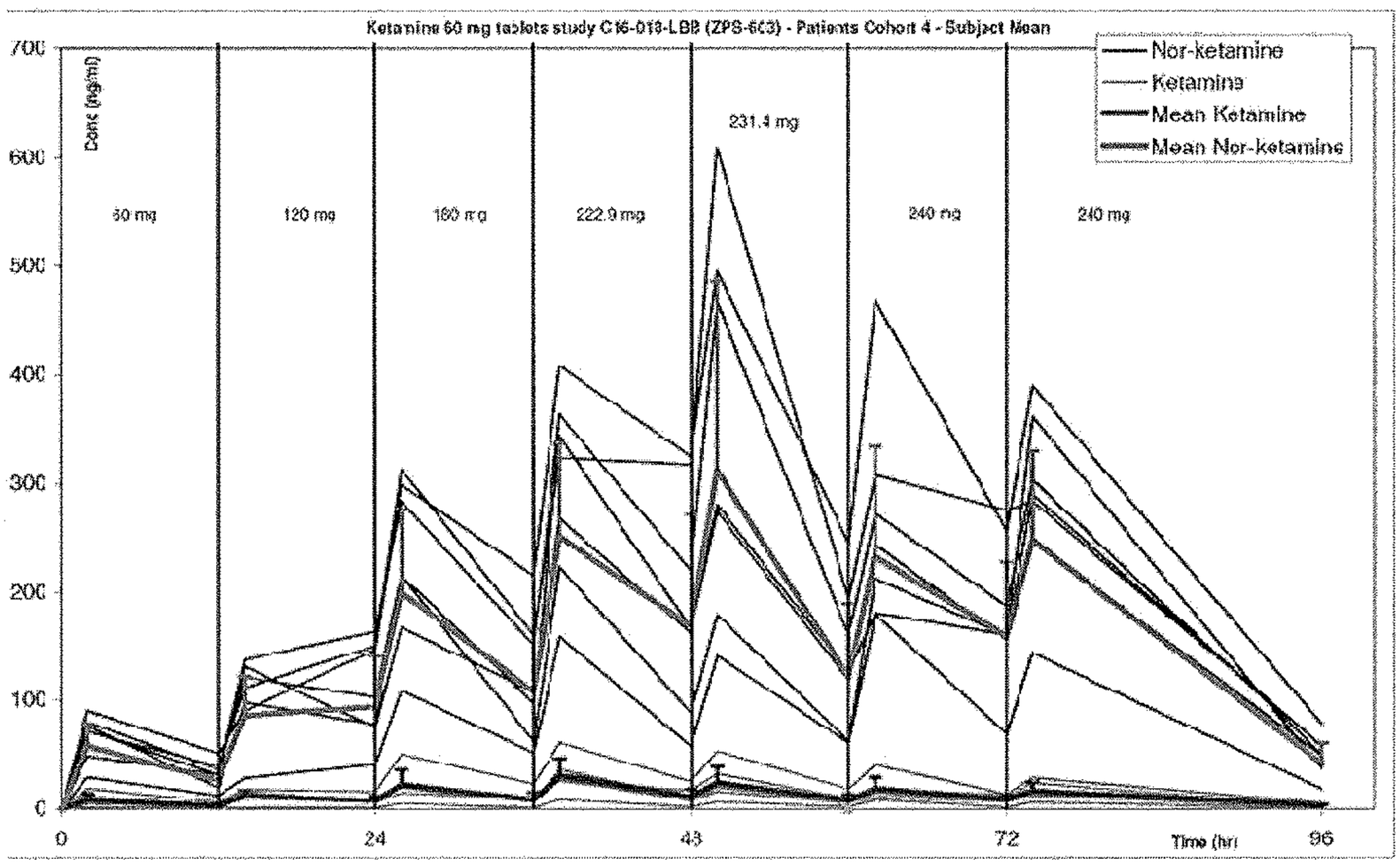
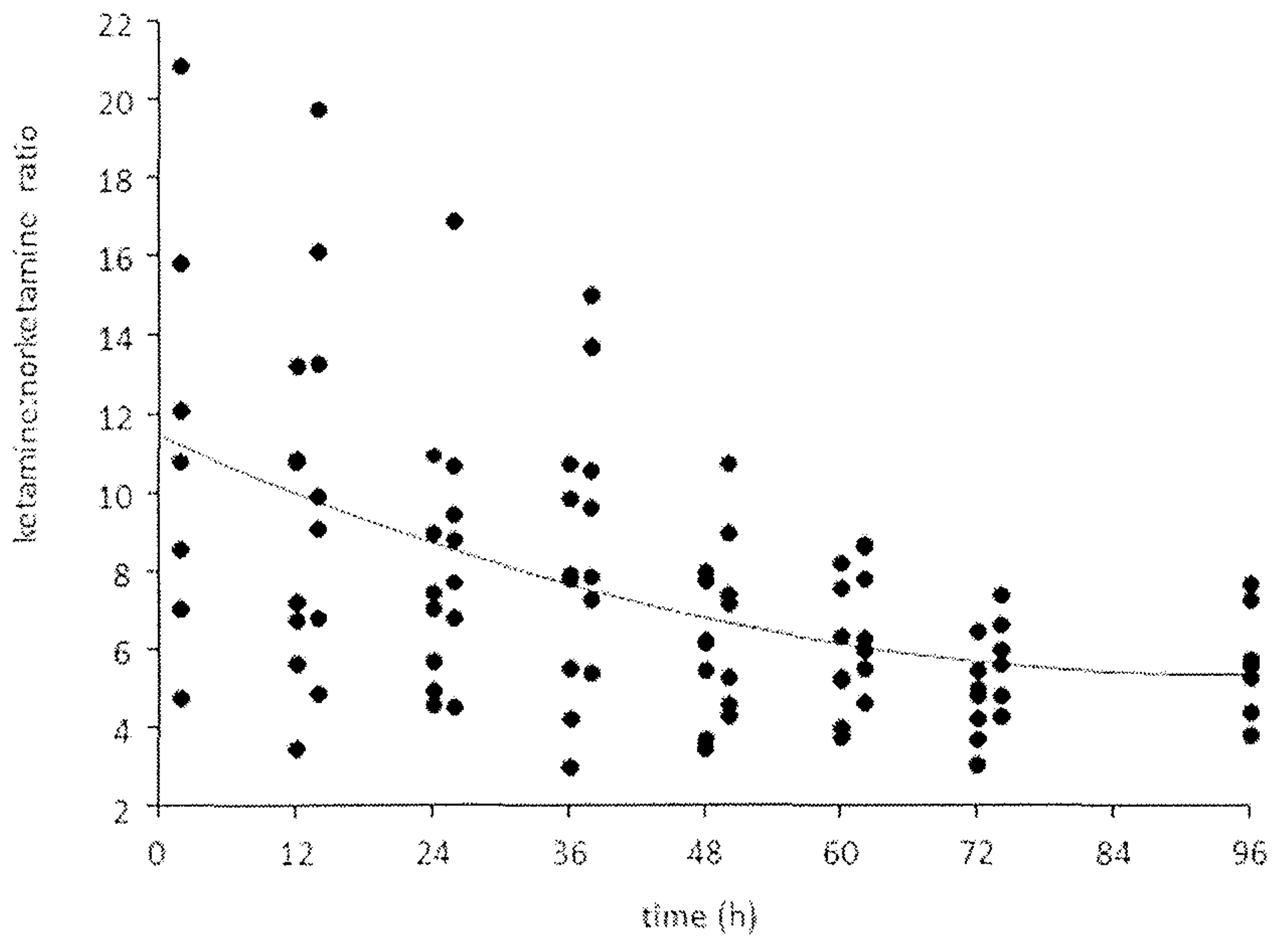

Ketamine 60 mg tablets study C16-019-LBB (ZPS-603) - Patients Cohort 4 - Subject Mean
Conc (ng/ml)
700
600
500
400
300
200
100
0
60 mg
120 mg
180 mg
222.9 mg
231.4 mg
240 mg
240 mg
Nor-ketamine
Ketamine
Mean Ketamine
Mean Nor-ketamine
0
24
48
72
Time (hr)
96

Figure 11


ketamine:norketamine ratio
22
20
18
16
14
12
10
8
6
4
2
0
12
24
36
48
60
72
84
96
time (h)

EXTENDED RELEASE PHARMACEUTICAL FORMULATION

BACKGROUND OF THE INVENTION

The initial report that low doses of the NMDA antagonist ketamine had rapid onset antidepressant effects in patients with treatment resistant depression (TRD; Berman 2000) has been confirmed in multiple subsequent studies (Xu 2016). More recently ketamine has been shown to have similar rapid-onset activity in a range of treatment-resistant anxiety (TRA) disorders including Post-Traumatic Stress Disorder (PTSD; Feder 2014), Obsessive Compulsive Disorder (OCD; Rodriguez 2013), Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD; Glue 2017). All of these studies have used injected ketamine, usually given intravenously. There are preliminary case series data suggesting that oral ketamine has antidepressant effects in patients with TRD (Schoevers 2016). The major side effects of injected ketamine include dissociative symptoms that occur mainly in the first hour after dosing, and minor increases in blood pressure and heart rate, which occur in the first 30 minutes. An oral ketamine formulation could minimize these side effects, and be less onerous/time consuming to administer than injected ketamine.

To explore the potential for an oral ketamine formulation to show activity in patients with TRD or TRA, the inventors developed an extended release ketamine tablet, using a hydrophilic polymeric matrix approach. Polyethylene oxide (PEO) is one of a number of hydrophilic polymers used in controlled drug delivery formulations, and has a number of positive attributes including nontoxicity, high water solubility and swellability (Maggi 2002). Furthermore, tablets formulations based on a high concentration of PEO are able to be annealed (heated) to give tablets of very high hardness that are resistant to crushing. This is a particularly attractive product attribute because ketamine is a drug of abuse. To minimize the potential for dissociative symptoms associated with rapid absorption of ketamine, a prolonged release profile was desirable. The formulation demonstrated linear in vitro dissolution over 10-12 hours. Elimination half-life estimates for ketamine and norketamine for this formulation are much longer that previously reported for tablets.

All references cited herein are incorporated herein by reference in their entireties.

BRIEF SUMMARY OF THE INVENTION

The invention provides a solid, oral, extended release pharmaceutical tablet comprising: (A) a core comprising: i) a therapeutically effective amount of an active agent selected from the group consisting of ketamine, norketamine, pharmaceutically acceptable salts thereof, and combinations thereof; ii) at least one high molecular weight polyethylene oxide (PEO) that is cured, wherein said high molecular weight PEO has an approximate molecular weight of from 2 million to 7 million, based upon rheological measurements, and is present in an amount of at least about 30% (by weight) of the core; (B) a coating on said core, wherein said tablet is crush resistant and has a breaking strength of at least about 200 N; and provides a mean t_{max} of said active agent at least about 4 hours after administration of a single tablet to a patient.

The invention provides a tablet wherein the molecular weight of said high molecular weight PEO is selected from the group consisting of at least about 4,000,000; at least about 5,000,000; at least about 6,000,000; and at least about 7,000,000. The invention provides a tablet wherein the active agent comprises at least about 1% (by weight) of the core. The invention provides a tablet wherein said high molecular weight PEO comprises at least about 50% (by weight) of said core. The invention provides a tablet wherein the dosage amount of active agent is selected from the group consisting of about 30 mg, about 60 mg, about 120 mg, and about 240 mg. The invention provides a tablet wherein the tablet is cured at a temperature of about 70° C. to about 75° C. The invention provides a tablet wherein the coating comprises: i) hydroxypropylmethylcellulose; ii) titanium dioxide; and iii) polyethylene glycol. The invention provides a tablet wherein said tablet provides a ketamine C_{max} between about 12 and about 42 ng/mL. The invention provides a tablet wherein said tablet provides a ketamine $AUC_{0\text{-}inf}$ between about 79 and about 385 ng·h/mL. The invention provides a tablet wherein said tablet provides a norketamine C_{max} between about 74 and about 315 ng/mL. The invention provides a tablet wherein said tablet provides a norketamine $AUC_{0\text{-}inf}$ between about 872 and about 4079 ng·h/mL. The invention provides a tablet wherein the mean t_{max} of said active agent is selected from the group consisting of at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 10 hours, at least about 11 hours, and at least about 12 hours. The invention provides a tablet wherein the tablet is suitable for once daily administration or twice-daily administration to a patient. The invention provides a tablet wherein the tablet has no or minimal dissociative side effects upon administration to a patient.

The invention provides a method of treating a patient for treatment-resistant depression, comprising: selecting a patient in need of such treatment; and orally administering to the patient a tablet comprising: (A) a core comprising: i) a therapeutically effective amount of an active agent selected from the group consisting of ketamine, norketamine, pharmaceutically acceptable salts thereof, and combinations thereof; ii) at least one high molecular weight polyethylene oxide (PEO) that is cured, wherein said high molecular weight PEO has an approximate molecular weight of from 2 million to 7 million, based upon rheological measurements, and is present in an amount of at least about 30% (by weight) of the core; (B) a coating on said core, wherein said tablet is crush resistant and has a breaking strength of at least about 200 N; and provides a mean t_{max} of said active agent at least about 4 hours after administration of a single tablet to a patient, wherein the tablet treats the symptoms of said treatment-resistant depression.

The invention provides a method wherein the molecular weight of said high molecular weight PEO is selected from the group consisting of at least about 2,000,000, at least about 4,000,000; at least about 5,000,000; at least about 6,000,000; and at least about 7,000,000. The invention provides a method wherein the active agent comprises at least about 1% (by weight) of the core. The invention provides a method wherein said high molecular weight PEO comprises at least about 50% (by weight) of said core. The invention provides a method wherein the dosage amount of active agent is selected from the group consisting of about 1 mg, about 2 mg, about 5 mg, about 10 mg, about 30 mg, about 60 mg, about 120 mg, and about 240 mg. 20. The invention provides a method wherein the tablet is cured at a temperature of about 70° C. to about 75° C. The invention provides a method wherein the coating comprises: i) hydroxypropylmethylcellulose; ii) titanium dioxide; and iii) polyethylene glycol. The invention provides a method wherein said tablet provides a ketamine C_{max} between about 12 and about 42 ng/mL. The invention provides a method

wherein said tablet provides a ketamine $AUC_{0\text{-}inf}$ between about 79 and about 385 ng·h/mL. The invention provides a method wherein said tablet provides a norketamine C_{max} between about 74 and about 315 ng/mL. The invention provides a method wherein said tablet provides a norketamine $AUC_{0\text{-}inf}$ between about 872 and about 4079 ng·h/mL. The invention provides a method wherein the mean t_{max} of said active agent is selected from the group consisting of at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 10 hours, at least about 11 hours, and at least about 12 hours. The invention provides a method wherein the tablet is suitable for once daily administration or twice-daily administration to a patient. The invention provides a method wherein the symptoms of said treatment-resistant depression are alleviated within 2 hours of oral administration of said ketamine. The invention provides a method wherein said method comprises oral administration of a single dose of said ketamine. The invention provides a method wherein said method comprises oral administration of multiple doses of said ketamine. The invention provides a method wherein a single oral administration of said ketamine in doses between 30-180 mg is sufficient to alleviate the effects of said depression for 3-7 days. The invention provides a method wherein tablet has no or minimal dissociative side effects in the patient. The invention provides a method wherein maximal mean improvements in ratings of depressed mood were noted after approximately 6 weeks of maintenance treatment. The invention provides a method further comprising administering a pharmaceutically effective dose of a second or additional agent, wherein said second or additional agent has antidepressant properties.

The invention provides a method wherein said method further comprises an additional therapy selected from: at least one antidepressant selected from the group consisting of citalopram, escitalopram oxalate, fluoxetine, fluvoxamine, paroxetine, sertraline, dapoxetine; venlafaxine and duloxetine; harmaline, iproniazid, isocarboxazid, nialamide, pargyline, phenelzine, selegiline, toloxatone, tranylcypromine, brofaromine, moclobemide; amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dibenzepin, dothiepin, doxepin, imipramine, iprindole, lofepramine, melitracen, nortriptyline, opipramol, protriptyline, trimipramine; maprotiline, mianserin, nefazodone, trazodone, pharmaceutically acceptable salts, isomers, and combinations thereof; at least one mood stabilizer selected from the group consisting of lithium carbonate, lithium orotate, lithium salt, valproic acid, divalproex sodium, sodium valproate, lamotrigine, carbamazepine, gabapentin, oxcarbazepine, topiramate, pharmaceutically acceptable salts, isomers, and combinations thereof; at least one herbal antidepressants selected from the group consisting of St John's Wort; kava kava; echinacea; saw palmetto; holy basil; valerian; milk thistle; Siberian ginseng; Korean ginseng; ashwagandha root; nettle; ginkgo biloba; gotu kola; ginkgo/gotu kola supreme; astragalus; goldenseal; dong quai; ginseng; St. John's wort supreme; echinacea; bilberry, green tea; hawthorne; ginger, gingko, turmeric; boswellia serata; black cohosh; cats claw; catnip; chamomile; dandelion; chaste tree berry; black elderberry; feverfew; garlic; horse chestnut; licorice; red clover blossom and leaf rhodiola rusa; coleus forskohlii; Passion Flower; eyebright; yohimbe; blueberry plant; black pepper plant; Hydrocotyle asiatica; astragalus; valerian poppy root and grape seed; vervain; echinacea ang root; Skull Cap; serenity elixir; and combinations thereof; at least one antipsychotic agent selected from the group consisting of haloperidol, chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, mesoridazine, promazine, triflupromazine, levomepromazine, promethazine, chlorprothixene, flupenthixol, thiothixene, zuclopenthixol, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, paliperidone, dopamine, bifeprunox, norclozapine, aripiprazole, tetrabenazine, cannabidiol, pharmaceutically acceptable salts, isomers, and combinations thereof; other therapeutic interventions selected from the group consisting of counseling, psychotherapy, cognitive therapy, electroconvulsive therapy, hydrotherapy, hyperbaric oxygen therapy, electrotherapy and electrical stimulation, transcutaneous electrical nerve stimulation ("TENS"), deep brain stimulation, vagus nerve stimulation, and transcranial magnetic stimulation, and combinations thereof.

The invention provides a method of treating a patient for treatment-resistant anxiety, including but not limited to DSM-V Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, Post-Traumatic Stress Disorder and/or Obsessive-Compulsive Disorder, comprising: selecting a patient in need of such treatment; and orally administering to the patient a tablet comprising: (A) a core comprising: i) a therapeutically effective amount of an active agent selected from the group consisting of ketamine, norketamine, pharmaceutically acceptable salts thereof, and combinations thereof; ii) at least one high molecular weight polyethylene oxide (PEO) that is cured, wherein said high molecular weight PEO has an approximate molecular weight of from 2 million to 7 million, based upon rheological measurements, and is present in an amount of at least about 30% (by weight) of the core; (B) a coating on said core, wherein said tablet is crush resistant and has a breaking strength of at least about 200 N; and provides a mean t_{max} of said active agent at least about 4 hours after administration of a single tablet to a patient, wherein the tablet treats the symptoms of said treatment-resistant anxiety. The invention provides a method wherein the molecular weight of said high molecular weight PEO is selected from the group consisting of at least about 2,000,000, at least about 4,000,000; at least about 5,000,000; at least about 6,000,000; and at least about 7,000,000. The invention provides a method wherein the active agent comprises at least about 1% (by weight) of the core. The invention provides a method wherein said high molecular weight PEO comprises at least about 50% (by weight) of said core. The invention provides a method wherein the dosage amount of active agent is selected from the group consisting of about 1 mg, about 2 mg, about 5 mg, about 10 mg, about 30 mg, about 60 mg, about 120 mg, and about 240 mg. The invention provides a method wherein the tablet is cured at a temperature of about 70° C. to about 75° C. The invention provides a method wherein the coating comprises: i) hydroxypropylmethylcellulose; ii) titanium dioxide; and iii) polyethylene glycol. The invention provides a method wherein said tablet provides a ketamine C_{max} between about 12 and about 42 ng/mL. The invention provides a method wherein said tablet provides a ketamine $AUC_{0\text{-}inf}$ between about 79 and about 385 ng·h/mL. The invention provides a method wherein said tablet provides a norketamine C_{max} between about 74 and about 315 ng/mL. The invention provides a method wherein said tablet provides a norketamine $AUC_{0\text{-}inf}$ between about 872 and about 4079 ng·h/mL. The invention provides a method wherein the mean t_{max} of said active agent is selected from the group consisting of at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 10 hours, at least about 11 hours, and at least about 12 hours. The invention provides a method wherein the tablet is suitable for once daily administration or

twice-daily administration to a patient. The invention provides a method wherein the tablet has no or minimal dissociative side effects upon administration to a patient. The invention provides a method wherein the symptoms of said treatment-resistant anxiety are alleviated within 2 hours of oral administration of said ketamine. The invention provides a method wherein said method comprises oral administration of a single dose of said ketamine. The invention provides a method wherein said method comprises oral administration of multiple doses of said ketamine. The invention provides a method wherein a single oral administration of said ketamine in doses between 30-180 mg is sufficient to alleviate the effects of said anxiety for 3-7 days. The invention provides a method wherein maximal mean improvements in ratings of anxious mood were noted after approximately 2 weeks of maintenance treatment. The invention provides a method further comprising administering a pharmaceutically effective dose of a second or additional agent, wherein said second or additional agent is has antianxiety properties. The invention provides a method which further comprises an additional therapy selected from: at least one antidepressant selected from the group consisting of citalopram, escitalopram oxalate, fluoxetine, fluvoxamine, paroxetine, sertraline, dapoxetine; venlafaxine and duloxetine; harmaline, iproniazid, isocarboxazid, nialamide, pargyline, phenelzine, selegiline, toloxatone, tranylcypromine, brofaromine, moclobemide; amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dibenzepin, dothiepin, doxepin, imipramine, iprindole, lofepramine, melitracen, nortriptyline, opipramol, protriptyline, trimipramine; maprotiline, mianserin, nefazodone, trazodone, pharmaceutically acceptable salts, isomers, and combinations thereof; at least one serotonin 1a partial agonist selected from the group consisting of buspirone, eltoprazine, or tandospirone, pharmaceutically acceptable salts, isomers, and combinations thereof; at least one alpha-2-delta ligand selected from the group consisting of gabapentin, pregabalin, 3-methyl-gabapentin, (1alpha,3 alpha,5alpha)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3 aminomethyl-5 methyl-heptanoic acid, (3S,5R)-3 amino-5 methyl-heptanoic acid, (3S,5R)-3 amino-5 methyl-octanoic acid, (2S, 4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0] hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S, 5R)-3 aminomethyl-5 methyl-octanoic acid, (3S,5R)-3 amino-5 methyl-nonanoic acid, (3S,5R)-3 amino-5 methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid, pharmaceutically acceptable salts, isomers, and combinations thereof; at least one antiadrenergic agents selected from the group consisting of clonidine, prazosin, propranolol, fuanfacine, methyldopa, guanabenz; doxazosin, prazosin, terazosin, silodosin, alfuzosin, tamsulosin, dutasertide/tamsulosin, guanadrel, mecemylamine, guanethidine, pharmaceutically acceptable salts, isomers, and combinations thereof; at least one benzodiazepine agent selected from the group consisting of alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, midazolam, lorazepam, nitrazepam, temazepam, nimetazepam, estazolam, flunitrazepam, oxazepam, triazolam, pharmaceutically acceptable salts, isomers, and combinations thereof; at least one antipsychotic agent selected from the group consisting of haloperidol, chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, mesoridazine, promazine, triflupromazine, levomepromazine, promethazine, chlorprothixene, flupenthixol, thiothixene, zuclopenthixol, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, paliperidone, dopamine, bifeprunox, norclozapine, aripiprazole, tetrabenazine, cannabidiol, pharmaceutically acceptable salts, isomers, and combinations thereof; other therapeutic interventions selected from the group consisting of counseling, psychotherapy, cognitive therapy, electroconvulsive therapy, hydrotherapy, hyperbaric oxygen therapy, electrotherapy and electrical stimulation, transcutaneous electrical nerve stimulation ("TENS"), deep brain stimulation, vagus nerve stimulation, and transcranial magnetic stimulation, and combinations thereof.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

The invention will be described in conjunction with the following drawings in which like reference numerals designate like elements and wherein:

FIG. **1** is a chart showing dissolution profiles of the 60 mg sustained release ketamine tablet at 3 different pHs.

FIG. **2**A is a chart showing the mean dissociation scale scores, using the Clinician-Administered Dissociative States Scale (CADSS) after a single dose of the sustained release tablet;

FIG. **2**B is a chart showing mean CADSS scores after multiple doses of the tablet, Cohorts 1-3.

FIG. **3**A is a chart showing mean concentration-time profiles of ketamine and norketamine after single dose, Cohorts 1-3; FIG. **3**B is a chart showing mean concentration-time profiles of ketamine and norketamine after multiple doses, Cohorts 1-3.

FIG. **4**A is a chart showing ketamine maximum concentration (Cmax) dose-proportionality after single doses of 60 mg, 120 mg and 240 mg extended release ketamine tablets; FIG. **4**B is a chart showing ketamine Area under the Concentration-Time curve (AUC) after single doses of 60 mg, 120 mg and 240 mg extended release ketamine tablets; FIG. **4**C is a chart showing ketamine maximum concentration (Cmax) dose-proportionality after multiple doses of 60 mg, 120 mg and 240 mg extended release ketamine tablets; FIG. **4**D is a chart showing ketamine Area under the Concentration-Time curve (AUC) after multiple doses of 60 mg, 120 mg and 240 mg extended release ketamine tablets; FIG. **4**E is a chart showing norketamine maximum concentration (Cmax) dose-proportionality after single doses of 60 mg, 120 mg and 240 mg extended release norketamine tablets; FIG. **4**F is a chart showing norketamine Area under the Concentration-Time curve (AUC) after single doses of 60 mg, 120 mg and 240 mg extended release norketamine tablets; FIG. **4**G is a chart showing norketamine maximum concentration (Cmax) dose-proportionality after multiple doses of 60 mg, 120 mg and 240 mg extended release norketamine tablets; FIG. **4**H is a chart showing norketamine Area under the Concentration-Time curve (AUC) after multiple doses of 60 mg, 120 mg and 240 mg extended release norketamine tablets, Cohorts 1-3.

FIG. **5**A is a chart showing the individual and mean CADSS scores, Cohort 4 after dosing with extended release ketamine tablets. FIG. **5**B is a chart showing the comparison of mean CADSS scores over 3 hours after initial dosing with ketamine tablets (filled symbols) and subcutaneous ketamine (open symbols) in the 6 Cohort 4 participants with both sets of data.

FIG. **6**A is a chart showing the individual and mean Hamilton Anxiety Scale (HAMA) scores, Cohort 4 after dosing with extended release ketamine tablets. FIG. **6**B is a chart showing the individual and mean Fear Questionnaire (FQ) scores, Cohort 4 after dosing with extended release ketamine tablets.

FIG. **7** is a chart showing comparison of mean HAMA scores after initial dosing with ketamine tablets (filled symbols) and subcutaneous ketamine (open symbols) in the 6 Cohort 4 participants with both sets of data.

FIG. **8** is a chart showing individual and mean Montgomery-Asberg Depression Rating Scale (MADRS) scores, Cohort 4 after dosing with extended release ketamine tablets.

FIG. **9**A is a chart showing the smoothed mean depression (MADRS) scores in 3 patients in Cohort 4, who entered a subsequent 3 month open-label extension (OLE) phase; FIG. **9**B is a chart showing anxiety (FQ) scores in the 3 patients in Cohort 4 who entered a subsequent 3 month open-label extension (OLE) phase; FIG. **9**C is a chart showing anxiety (HAMA) scores in the 3 patients in Cohort 4 who entered a subsequent 3 month open-label extension (OLE) phase. All three patients reported improvements in mood ratings during this time. Mean depression ratings appeared to take 6 weeks for maximal improvement (FIG. **9**A), whereas mean maximal anxiety scale improvement appeared to occur by week **2** (FIGS. **9**B, **9**C).

FIG. **10** is a chart showing individual and mean concentration-time profiles of ketamine and norketamine, Cohort 4. Mean dose administered at each 12 hour interval is shown above the concentration-time plots.

FIG. **11** is a chart showing changes in individual ketamine:norketamine ratios associated with 12 hourly dosing of extended release ketamine tablets, with a fitted regression line, Cohort 4.

DETAILED DESCRIPTION OF THE INVENTION

As used herein the term "active pharmaceutical ingredient" ("API") or "pharmaceutically active agent" is a drug or agent which can be employed for the invention and is intended to be used in the human or animal body in order to heal, to alleviate, to prevent or to diagnose diseases, ailments, physical damage or pathological symptoms; allow the state, the condition or the functions of the body or mental states to be identified; to replace active substances produced by the human or animal body, or body fluids; to defend against, to eliminate or to render innocuous pathogens, parasites or exogenous substances or to influence the state, the condition or the functions of the body or mental states. Drugs in use can be found in reference works such as, for example, the Rote Liste or the Merck Index. Examples which may be mentioned include ketamine.

An amount is "effective" as used herein, when the amount provides an effect in the subject. As used herein, the term "effective amount" means an amount of a compound or composition sufficient to significantly induce a positive benefit, including independently or in combinations the benefits disclosed herein, but low enough to avoid serious side effects, i.e., to provide a reasonable benefit to risk ratio, within the scope of sound judgment of the skilled artisan. For those skilled in the art, the effective amount, as well as dosage and frequency of administration, may easily be determined according to their knowledge and standard methodology of merely routine experimentation based on the present disclosure.

As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, the term "patient" refers to an animal, preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey and human), and most preferably a human. In some embodiments, the subject is a non-human animal such as a farm animal (e.g., a horse, pig, or cow) or a pet (e.g., a dog or cat). In a specific embodiment, the subject is an elderly human. In another embodiment, the subject is a human adult. In another embodiment, the subject is a human child. In yet another embodiment, the subject is a human infant.

As used herein, the phrase "pharmaceutically acceptable" means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia, or other generally recognized pharmacopeia for use in animals, and more particularly, in humans.

As used herein, the terms "prevent," "preventing" and "prevention" in the context of the administration of a therapy to a subject refer to the prevention or inhibition of the recurrence, onset, and/or development of a disease or condition, or a combination of therapies (e.g., a combination of prophylactic or therapeutic agents).

As used herein, the terms "therapies" and "therapy" can refer to any method(s), composition(s), and/or agent(s) that can be used in the prevention, treatment and/or management of a disease or condition, or one or more symptoms thereof.

As used herein, the terms "treat," "treatment," and "treating" in the context of the administration of a therapy to a subject refer to the reduction or inhibition of the progression and/or duration of a disease or condition, the reduction or amelioration of the severity of a disease or condition, and/or the amelioration of one or more symptoms thereof resulting from the administration of one or more therapies.

As used herein, the term "about" when used in conjunction with a stated numerical value or range has the meaning reasonably ascribed to it by a person skilled in the art, i.e. denoting somewhat more or somewhat less than the stated value or range.

Depression is characterized by depressed mood, and markedly diminished interest or pleasure in activities. Other symptoms include significant weight loss or weight gain, decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate or indecisiveness, recurrent thoughts of death, suicidal ideation or suicidal attempts.

A variety of somatic symptoms may also be present. Though depressive feelings are common, especially after experiencing setbacks in life, depressive disorder is diagnosed only when the symptoms reach a threshold and last at least two weeks. Depression can vary in severity from mild to very severe. It is most often episodic but can be recurrent or chronic. Some people have only a single episode, with a full return to premorbid function. However, more than 50 percent of those who initially suffer a single major depressive episode eventually develop another.

Treatment resistant-depression includes unipolar depression that does not respond satisfactorily to one or more treatments that are optimally delivered. If the depression has not benefited from at least two adequate trials of medications from different classes in the current episode, clinically significant treatment resistance is present.

Any chronic, treatment-resistant depression may be treated by the methods described herein. Such depression may include but is not limited to any of: major depressive disorder, single episode, recurrent major depressive disor-

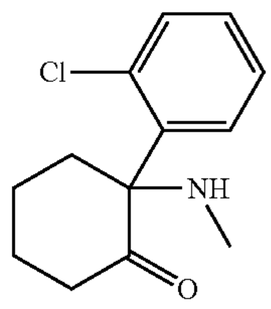
der-unipolar depression, seasonal affective disorder-winter depression, bipolar mood disorder-bipolar depression, mood disorder due to a general medical condition—with major depressive-like episode, or mood disorder due to a general medical condition—with depressive features, wherein those disorders are resistant to treatment in a given patient. Thus, any patient that presents one of those disorders and who has not responded to an adequate trial of one antidepressant in the current episode and has recurrent or chronic depressive symptoms for greater than 2 years can be treated by the methods of the invention. Manic Depressive illnesses are also described in Goodwin, et al. 2007.

Anxiety is a mood disorder characterized by nervousness, fear, apprehension, and worrying. Patients with anxiety disorders may report symptoms such as excessive worry, panic attacks, or avoidance of specific situations (e.g. social interactions, supermarkets). Treatment resistant anxiety (TRA; anxiety that has not resolved or improved despite adequate medication and psychotherapy) is relatively common, with approximately 30% of patients showing no response to treatment, and a further 30-40% of patients having a partial response (Brown 1996). No drug treatments are approved at present for TRA.

Autoinduction is the ability of a drug to induce enzymes that enhance its own metabolism, which may result in tolerance.

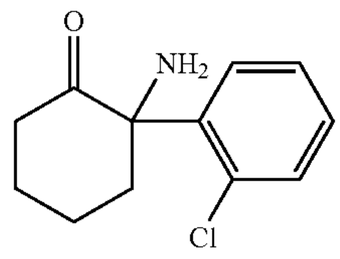
Active Agent

The pharmaceutical composition of the invention may comprise an active agent, selected from the group consisting of, for example, ketamine, norketamine, pharmaceutically acceptable salts thereof, and combinations thereof. "Ketamine" as used herein is understood to comprise the compound of formula (I)



having the IUPAC name 2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one. Accordingly, ketamine comprises the R and S enantiomers as well as pharmaceutically acceptable salts or solvates thereof. In one embodiment, ketamine is (R)-ketamine or pharmaceutically acceptable salts or solvates thereof. In another embodiment, ketamine is (S)-ketamine or pharmaceutically acceptable salts or solvates thereof. In a further embodiment, ketamine is a racemate of (S)-ketamine and (R)-ketamine or pharmaceutically acceptable salts or solvates thereof, or any mixture of (S)-ketamine and (R)-ketamine or pharmaceutically acceptable salts or solvates thereof. Ketamine can preferably comprise the pharmaceutically acceptable acid addition salts thereof. The acids which are used to prepare the pharmaceutically acceptable acid addition salts are preferably those which form non-toxic acid addition salts, i.e. salts containing pharmacologically acceptable anions, such as chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, (D,L)- and L-tartrate, (D,L)- and L-malate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate and benzoate. A preferred salt is the hydrochloride of ketamine.

Ketamine as used herein can also comprise its metabolites. The metabolite is norketamine or dehydronorketamine, preferably norketamine. Norketamine has the IUPAC name 2-amino-2-(2-chlorophenyl)cyclohexan-1-one of formula (II)



and is obtained from ketamine through N-demethylation. Norketamine can be provided as (R)-norketamine or pharmaceutically acceptable salts or solvates thereof, or (S)-norketamine or pharmaceutically acceptable salts or solvates thereof, racemate of (S)-norketamine and (R)-norketamine or pharmaceutically acceptable salts or solvates thereof, or any mixture of (S)-norketamine and (R)-norketamine or pharmaceutically acceptable salts or solvates thereof.

In exemplary embodiments, formulations of the invention may comprise active agent at a concentration of about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%. In exemplary embodiments, formulations of the invention may comprise active agent at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%.

Combination Therapy

Methods and compositions of treating and/or preventing a condition in a subject are provided according to embodiments of the present invention which include administering, in combination, a compound of the invention as set forth herein and at least one additional therapy, such as a therapeutic agent selected from the group consisting of at least one anti-anxiety drug, at least one anti-depressant drug, at least one neuroleptic medication, at least one mood stabilizer drug, at least one antipsychotic drug, at least one hypnotic, and combinations thereof. In exemplary embodiments, the active agent is administered in combination with or concurrently with another therapeutic intervention to enhance the efficacy thereof. Examples of other therapeutic interventions include, but are not limited to, counseling, psychotherapy, cognitive therapy or the like, electroconvulsive therapy, hydrotherapy, hyperbaric oxygen therapy, electrotherapy and electrical stimulation, transcutaneous electrical nerve stimulation or "TENS" (e.g., for the treatment of pain such as neuropathic pain), deep brain stimulation (e.g., for the treatment of pain such as neuropathic pain, Parkinson's disease, tremor, dystonia, etc.), vagus nerve stimulation and/or transcranial magnetic stimulation, etc.

In exemplary embodiments, at least one anti-anxiety drug is alprazolam, bromazepam, diazepam, lorazepam, clonazepam, temazepam, oxazepam, flunitrazepam, triazolam, chlordiazepoxide, flurazepam, estazolam, nitrazepam, and pharmaceutically acceptable salts, isomers, and mixtures thereof. Further examples of anxiolytic drugs include, but are not limited to, benzodiazepines (e.g., alprazolam, bromazepam (LEXOTAN), chlordiazepoxide (LIBRIUM), clobazamclobazam, clonazepam, clorazepate, diazepam,

midazolam, lorazepam, nitrazepam, nimetazepam, estazolam, flunitrazepam, oxazepam (Serax), temazepam (RESTORIL, NORMISON, PLANUM, TENOX, and TEMAZE), triazolam, serotonin 1A agonists (e.g., buspirone (BUSPAR)), barbiturates (e.g., amobarbital (amytal sodium), pentobarbital (NEMBUTAL), secobarbital (SECONAL), phenobarbital, methohexital, thiopental, methylphenobarbital, metharbital, barbexaclone), hydroxyzine, cannabidiol, and herbal treatments. (e.g., valerian, kava (Kava Kava), chamomile, Kratom, Blue Lotus extracts, Sceletium tortuosum (kanna) and Bacopa monniera).

In exemplary embodiments, at least one anti-depressant drug is citalopram, escitalopram oxalate, fluoxetine, fluvoxamine, paroxetine, sertraline, dapoxetine; venlafaxine and duloxetine; harmaline, iproniazid, isocarboxazid, nialamide, pargyline, phenelzine, selegiline, toloxatone, tranylcypromine, brofaromine, moclobemide; amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dibenzepin, dothiepin, doxepin, imipramine, iprindole, lofepramine, melitracen, nortriptyline, opipramol, protriptyline, trimipramine; maprotiline, mianserin, nefazodone, trazodone, and pharmaceutically acceptable salts, isomers, and combinations thereof. Anti-depressant medications include synthesized chemical compounds as well as naturally occurring or herbal remedies such as St. John's Wort.

Herbal antidepressants may include, for example, St John's Wort; kava kava; echinacea; saw palmetto; holy basil; valerian; milk thistle; Siberian ginseng; Korean ginseng; ashwagandha root; nettle; ginkgo biloba; gotu kola; ginkgo/gotu kola supreme; astragalus; goldenseal; dong quai; ginseng; St. John's wort supreme; echinacea; bilberry, green tea; hawthorne; ginger, gingko, turmeric; boswellia serata; black cohosh; cats claw; catnip; chamomile; dandelion; chaste tree berry; black elderberry; feverfew; garlic; horse chestnut; licorice; red clover blossom and leaf rhodiola rusa; coleus forskohlii; Passion Flower; eyebright; yohimbe; blueberry plant; black pepper plant; Hydrocotyle asiatica; astragalus; valerian poppy root and grape seed; vervain; echinacea ang root; Skull Cap; serenity elixir; and combinations thereof.

Examples of antidepressants include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine (PROZAC), paroxetine (PAXIL, SEROXAT), escitalopram (LEXAPRO, ESIPRAM), citalopram (CELEXA), and sertraline (ZOLOFT)), serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine (EFFEXOR), and duloxetine (CYMBALTA)), noradrenergic and specific serotonergic antidepressants (NASSAs) (e.g., mirtazapine (AVANZA, ZISPIN, REMERON)), norepinephrine (noradrenaline) reuptake inhibitors (NRIs) (e.g., reboxetine (EDRONAX)), norepinephrine-dopamine reuptake inhibitors (e.g., bupropion (WELLBUTRIN, ZYBAN)), tricyclic antidepressants (TCAs) (e.g., amitriptyline and desipramine), monoamine oxidase inhibitor (MAOIs) (e.g., phenelzine (NARDIL), moclobemide (MANERIX), selegiline), and augmentor drugs (e.g., tryptophan (TRYPTAN) and buspirone (BUSPAR)).

In exemplary embodiments, at least one neuroleptic drug is haloperidol (HALDOL), droperidol, benperidol, triperidol, melperone, lenperone, azaperone, domperidone, risperidone, chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, mesoridazine, periciazine, promazine, triflupromazine, levomepromazine, promethazine, pimozide, cyamemazine, chlorprothixene, clopenthixol, flupenthixol, thiothixene, zuclopenthixol, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, asenapine, paliperidone, iloperidone, zotepine, sertindole, lurasidone, aripiprazole, and pharmaceutically acceptable salts, isomers, and combinations thereof,

In exemplary embodiments, at least one mood stabilizer drugs includes, but is not limited to, Lithium carbonate, lithium orotate, lithium salt, Valproic acid (DEPAKENE), divalproex sodium (DEPAKOTE), sodium valproate (DEPACON), Lamotrigine (LAMICTAL), Carbamazepine (TEGRETOL), Gabapentin (NEURONTIN), Oxcarbazepine (TRILEPTAL), and Topiramate (TOPAMAX), and combinations thereof.

Examples of antipsychotic drugs include, but are not limited to, butyrophenones (e.g., haloperidol), phenothiazines (e.g., chlorpromazine (THORAZINE), fluphenazine (PROLIXIN), perphenazine (TRILAFON), prochlorperazine (COMPAZINE), thioridazine (MELLARIL), trifluoperazine (STELAZINE), mesoridazine (SERENTIL), promazine, triflupromazine (VESPRIN), levomepromazine (NOZINAN), promethazine (PHENERGAN)), thioxanthenes (e.g., chlorprothixene (TRUXAL), flupenthixol (DEPIXOL and FLUANXOL), thiothixene (NAVANE), zuclopenthixol (CLOPIXOL & ACUPHASE)), clozapine, olanzapine, risperidone (RISPERDAL), quetiapine (SEROQUEL), ziprasidone (GEODON), amisulpride (SOLIAN), paliperidone (INVEGA), dopamine, bifeprunox, norclozapine (ACP-104), Aripiprazole (ABILIFY), tetrabenazine (XENAZINE), and cannabidiol and pharmaceutically acceptable salts, isomers, and combinations thereof.

Examples of hypnotics include, but are not limited to, barbiturates, opioids, benzodiazepines (e.g., alprazolam, bromazepam (Lexotan), chlordiazepoxide (Librium), clobazam, clonazepam, clorazepate, diazepam, midazolam, lorazepam, nitrazepam, nimetazepam, estazolam, flunitrazepam, oxazepam (SERAX), temazepam (RESTORIL, NORMISON, PLANUM, TENOX, and TEMAZE), triazolam), nonbenzodiazepines (e.g., ZOLPIDEM, ZALEPLON, ZOPICLONE, ESZOPICLONE), antihistamines (e.g., diphenhydramine, doxylamine, hydroxyzine, promethazine), gamma-hydroxybutyric acid (Xyrem), Glutethimide, Chloral hydrate, Ethchlorvynol, Levomepromazine, Chlormethiazole, Melatonin, and Alcohol. Examples of sedatives include, but are not limited to, barbituates (e.g., amobarbital (Amytal), pentobarbital (Nembutal), secobarbital (Seconal), phenobarbital, methohexital, thiopental, methylphenobarbital, metharbital, barbexaclone), benzodiazepines (e.g., alprazolam, bromazepam (LEXOTAN), chlordiazepoxide (LIBRIUM), clobazam, clonazepam, clorazepate, diazepam, midazolam, lorazepam, nitrazepam, nimetazepam, estazolam, flunitrazepam, oxazepam (SERAX), temazepam (RESTORIL, NORMISON, PLANUM, TENOX, and TEMAZE), triazolam), and pharmaceutically acceptable salts, isomers, and combinations thereof. Examples further include Herbal sedatives (e.g., ashwagandha, catnip, kava (*Piper methysticum*), mandrake, marijuana, valerian),solvent sedatives (e.g., chloral hydrate (NOCTEC), diethyl ether (Ether), ethyl alcohol (alcoholic beverage), methyl trichloride (chloroform)), nonbenzodiazepine sedatives (e.g., eszopiclone (LUNESTA), zaleplon (SONATA), zolpidem (AMBIEN), zopiclone (IMOVANE, ZIMOVANE)), clomethiazole, gamma-hydroxybutyrate (GHB), thalidomide, ethchlorvynol (PLACIDYL), glutethimide (DORIDEN), ketamine (KETALAR, KETASET), methaqualone (SOPOR, QUAALUDE), methyprylon (NOLUDAR), and ramelteon (ROZEREM).

Examples of alpha-2-delta ligand include gabapentin, pregabalin, 3-methylgabapentin, (1alpha,3 alpha,5alpha)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S, 5R)-3 aminomethyl-5 methyl-heptanoic acid, (3S,5R)-3

amino-5 methyl-heptanoic acid, (3S,5R)-3 amino-5 methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3 aminomethyl-5 methyl-octanoic acid, (3S,5R)-3 amino-5 methyl-nonanoic acid, (3S,5R)-3 amino-5 methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid, and combinations thereof.

Examples of serotonin 1a partial agonist include buspirone, gepirone, eltoprazine, or tandospirone, pharmaceutically acceptable salts, isomers, and combinations thereof.

Examples of antiadrenergic agents include clonidine, prazosin, propranolol, fuanfacine, methyldopa, guanabenz; doxazosin, prazosin, terazosin, silodosin, alfuzosin, tamsulosin, dutasertide/tamsulosin, guanadrel, mecemylamine, guanethidine, pharmaceutically acceptable salts, isomers, and combinations thereof.

Examples of benzodiazepine agents include alprazolam, bromazepam (LEXOTAN), chlordiazepoxide (LIBRIUM), clobazam, clonazepam, clorazepate, diazepam, midazolam, lorazepam, nitrazepam, nimetazepam, estazolam, flunitrazepam, oxazepam (SERAX), temazepam (RESTORIL, NORMISON, PLANUM, TENOX, and TEMAZE), triazolam, pharmaceutically acceptable salts, isomers, and combinations thereof.

The agents are administered in therapeutically effective amounts. In certain embodiments the agents are administered in the same dosage form. In certain embodiments the therapeutic agents are administered separately.

Pharmacokinetics

The formulation of the invention provides extended release of ketamine of, for example, over 4 hours, over 5 hours, over 6 hours, over 7 hours, over 8 hours, over 9 hours, over 10 hours, or more. Elimination half-life estimates for ketamine and norketamine for the formulation as set forth herein are much longer that previously reported for immediate release tablet formulations (e.g. 8 h vs <2 h; Yanagihara 2002)

There is evidence that the formulations of the invention provide for autoinduction (FIG. **10**). This appears to have stabilized after 3-4 days of repeat dosing. There is no prior human data on this.

There is evidence for the formulations of the invention that over 90% of the absorbed drug is present as norketamine rather than ketamine. In the patient cohort (cohort 4) there were improvements in depression and anxiety despite the major measurable drug present being norketamine. There has been much discussion in the scientific literature about whether ketamine or a metabolite are important in producing improvements in mood after dosing with ketamine. Zanos 2016 and Zarate 2017 highlight ketamine's metabolite, 6-hydroxy norketamine as important. The inventors have surprisingly found that norketamine itself is important in the tablet's therapeutic effects. This is in contrast to a previous report which presented data as combined ketamine and norketamine, rather than separately, and did not report on the importance of norketamine to the therapeutic effect. (See WO 2015/031410).

The oral formulation as set forth herein has no dissociative side effects after 60-120 mg doses, and minimal dissociative side effects at 240 mg (FIGS. **2**A and **2**B). This contrasts markedly with injected ketamine by any route of administration (e.g. Loo 2016), where there are marked dissociative symptoms for up to 60 minutes after dosing.

There is evidence that the formulations of the invention are efficacious in improving both depressed and anxious mood, with improved tolerability compared with injected ketamine. For example, a leading research group has highlighted a finding that having a dissociative experience is critical to mood improvement in TRD. "Among the examined mediators of ketamine's antidepressant response, only dissociative side effects predicted a more robust and sustained antidepressant" (www.ncbi.nlm.nih.gov/pubmed/24679390). The inventors have found that improvement in depression scores occurs with no or minimal dissociation (see FIGS. **8** and **5**A). This observation of improvement in depression scores in the absence of dissociation is novel and nonobvious.

The onset of improvement of anxiety symptoms in study 603 cohort 4 was more gradual (48h) compared with 1-2h for injected ketamine (FIG. **7**), however the same overall magnitude of effect was observed as with injected drug in earlier treatment.

Furthermore, a safe and effective dose and dosing scheduled have been identified in an open-label extension study for patients who completed the 603 study. Three of 4 patients with mixed anxiety/depressive disorders remained in remission on doses of 120 mg orally once or twice weekly.

This has been accomplished by preparing the sustained release formulation in such a manner that the active agent is released more favorably in low pH (e.g., gastric fluid) rather than high pH (e.g., intestinal fluid).

Matrix Formulations

In certain embodiments, the present invention is directed to a process of preparing a solid oral extended release pharmaceutical dosage form, comprising at least the steps of:

(a) combining:

(1) at least one polyethylene oxide having, based on rheological measurements, an approximate molecular weight selected from the group consisting of at least about 1,000,000; at least about 2,000,000; at least about 3,000,000; at least about 4,000,000; at least about 5,000,000; at least about 6,000,000; at least about 6,000,000; at least about 7,000,000; and at least about 8,000,000; and

(2) at least one active agent, to form a composition;

(b) shaping the composition to form an extended release matrix formulation; and

(c) curing said extended release matrix formulation comprising at least a curing step of subjecting the extended release matrix formulation to a temperature which is at least the softening temperature of said polyethylene oxide for a time period selected from the group consisting of at least about 1 minute, at least about 2 minutes, at least about 3 minutes, at least about 4 minutes, at least about 5 minutes, at least about 6 minutes, at least about 7 minutes, at least about 8 minutes, at least about 9 minutes, and at least about 10 minutes. Preferably, the curing is conducted at atmospheric pressure. In a preferred embodiment the dosage form is coated.

In certain embodiments the composition is shaped in step b) to form an extended release matrix formulation in the form of tablet. For shaping the extended release matrix formulation in the form of tablet a direct compression process can be used. Direct compression is an efficient and simple process for shaping tablets by avoiding process steps like wet granulation. However, any other process for manu-

facturing tablets as known in the art may be used, such as wet granulation and subsequent compression of the granules to form tablets.

In one embodiment, the curing of the extended release matrix formulation in step c) comprises at least a curing step wherein the high molecular weight polyethylene oxide in the extended release matrix formulation at least partially melts. For example, at least about 20% or at least about 30% of the high molecular weight polyethylene oxide in the extended release matrix formulation melts. Preferably, at least about 40% or at least about 50%, more preferably at least about 60%, at least about 75% or at least about 90% of the high molecular weight polyethylene oxide in the extended release matrix formulation melts. In a preferred embodiment, about 100% of the high molecular weight polyethylene oxide melts.

In other embodiments, the curing of the extended release matrix formulation in step c) comprises at least a curing step wherein the extended release matrix formulation is subjected to an elevated temperature for a certain period of time. In such embodiments, the temperature employed in step c), i.e. the curing temperature, is at least as high as the softening temperature of the high molecular weight polyethylene oxide. Without wanting to be bound to any theory it is believed that the curing at a temperature that is at least as high as the softening temperature of the high molecular weight polyethylene oxide causes the polyethylene oxide particles to at least adhere to each other or even to fuse. According to some embodiments the curing temperature is at least about 60° C. or at least about 62° C., or ranges from about 62° C., to about 90° C., or from about 62° C. to about 85° C. or from about 62° C. to about 80° C. or from about 65° C. to about 90° C. or from about 65° C. to about 85° C. or from about 65° C. to about 80° C. The curing temperature preferably ranges from about 68° C. to about 90° C. or from about 68° C. to about 85° C. or from about 68° C. to about 80° C., more preferably from about 70° C. to about 90° C. or from about 70° C. to about 85° C. or from about 70° C. to about 80° C., most preferably from about 75° C. to about 90° C. or from about 75° C. to about 85° C. or from about 72° C. to about 80° C., or from about 70° C. to about 75° C. The curing temperature may be at least about 60° C. or at least about 62° C., but less than about 90° C. or less than about 80° C. Preferably, it is in the range of from about 62° C. to about 75° C., in particular from about 68° C. to about 75° C. Preferably, the curing temperature is at least as high as the lower limit of the softening temperature range of the high molecular weight polyethylene oxide or at least about 62° C. or at least about 68° C. More preferably, the curing temperature is within the softening temperature range of the high molecular weight polyethylene oxide or at least about 70° C. Even more preferably, the curing temperature is at least as high as the upper limit of the softening temperature range of the high molecular weight polyethylene oxide or at least about 72° C. In an alternative embodiment, the curing temperature is higher than the upper limit of the softening temperature range of the high molecular weight polyethylene oxide, for example the curing temperature is at least about 75° C. or at least about 80° C.

The curing time may vary from about 1 minute to about 24 hours or from about 5 minutes to about 20 hours or from about 10 minutes to about 15 hours or from about 15 minutes to about 10 hours or from about 30 minutes to about 5 hours depending on the specific composition and on the formulation and the curing temperature. The parameter of the composition, the curing time and the curing temperature are chosen to achieve the tamper resistance as described herein. According to certain embodiments the curing time varies from about 15 minutes to about 30 minutes.

In certain embodiments of the present invention, the sustained release formulation may be achieved via a matrix optionally having a controlled release coating as set forth herein. The present invention may also utilize a sustained release matrix that affords in-vitro dissolution rates of the API within desired ranges and releases the API in a pH-dependent or pH-independent manner.

A non-limiting list of suitable sustained-release materials which may be included in a sustained-release matrix according to the invention includes hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials, waxes, shellac, and oils such as hydrogenated castor oil and hydrogenated vegetable oil. However, any pharmaceutically acceptable hydrophobic or hydrophilic sustained-release material which is capable of imparting sustained-release of the API may be used in accordance with the present invention. Preferred sustained-release polymers include alkylcelluloses such as ethylcellulose, acrylic and methacrylic acid polymers and copolymers; and cellulose ethers, especially hydroxyalkylcelluloses (especially hydroxypropylmethylcellulose) and carboxyalkylcelluloses. Preferred acrylic and methacrylic acid polymers and copolymers include methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, ethyl acrylate, trimethyl ammonioethyl methacrylate, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly (acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methylmethacrylate), poly (methacrylic acid) (anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Certain preferred embodiments utilize mixtures of any of the foregoing sustained-release materials in the matrix of the invention. The matrix also may include a binder.

In addition to the above ingredients, a sustained-release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids and glidants that are conventional in the pharmaceutical art.

A sustained-release matrix can be prepared by, e.g., melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic binder material, e.g., a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate a hydrophobic sustained-release material, e.g., ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic binder material.

The additional hydrophobic binder material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve sustained release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like binder substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the API with a sustained release material and preferably a binder material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous

mixture is then extruded, e.g., using a twin-screw extruder, to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The matrix multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the active agent or pharmaceutically acceptable salt thereof for a time period of at least about 24 hours.

An optional process for preparing the melt extruded formulations of the present invention includes directly metering into an extruder a hydrophobic sustained release material, the API, and an optional binder material; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into matrix multiparticulates having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

Plasticizers, such as those described above, may be included in melt-extruded matrices. The plasticizer is preferably included as from about 0.1 to about 30% by weight of the matrix. Other pharmaceutical excipients, e.g., talc, mono or poly saccharides, lubricants and the like may be included in the sustained release matrices of the present invention as desired. The amounts included will depend upon the desired characteristic to be achieved.

The diameter of the extruder aperture or exit port can be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

A melt extruded matrix multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded matrix multiparticulate(s)" and "melt-extruded matrix multiparticulate system(s)" and "melt-extruded matrix particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic sustained release material as described herein. Preferably the melt-extruded matrix multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded matrix multiparticulates can be any geometrical shape within this size range. In certain embodiments, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared that include an effective amount of melt-extruded matrix multiparticulates within a capsule. For example, a plurality of the melt-extruded matrix multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastrointestinal fluid.

In another embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).

In addition to the above ingredients, the spheroids, granules, or matrix multiparticulates may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the formulation if desired. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

In one embodiment, at least one active agent in solubility-improved form is incorporated into an erodible or non-erodible polymeric matrix controlled release device. By an erodible matrix is meant aqueous-erodible or water-swellable or aqueous-soluble in the sense of being either erodible or swellable or dissolvable in pure water or requiring the presence of an acid or base to ionize the polymeric matrix sufficiently to cause erosion or dissolution. When contacted with the aqueous environment of use, the erodible polymeric matrix imbibes water and forms an aqueous-swollen gel or "matrix" that entraps the solubility-improved form of the active agent. The aqueous-swollen matrix gradually erodes, swells, disintegrates or dissolves in the environment of use, thereby controlling the release of the active agent to the environment of use. The erodible polymeric matrix into which the active agent is incorporated may generally be described as a set of excipients that are mixed with the solubility-improved form following its formation that, when contacted with the aqueous environment of use imbibes water and forms a water-swollen gel or "matrix" that entraps the drug form. Drug release may occur by a variety of mechanisms: the matrix may disintegrate or dissolve from around particles or granules of the drug in solubility-improved form; or the drug may dissolve in the imbibed aqueous solution and diffuse from the tablet, beads or granules of the device. A key ingredient of this water-swollen matrix is the water-swellable, erodible, or soluble polymer, which may generally be described as an osmopolymer, hydrogel or water-swellable polymer. Such polymers may be linear, branched, or crosslinked. They may be homopolymers or copolymers. Although they may be synthetic polymers derived from vinyl, acrylate, methacrylate, urethane, ester and oxide monomers, they are most preferably derivatives of naturally occurring polymers such as polysaccharides or proteins.

Such materials include naturally occurring polysaccharides such as chitin, chitosan, dextran and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum and scleroglucan; starches such as dextrin and maltodextrin; hydrophilic colloids such as pectin; phosphatides such as lecithin; alginates such as ammonium alginate, sodium, potassium or calcium alginate, propylene glycol alginate; gelatin; collagen; and cellulosics. By "cellulosics" is meant a cellulose polymer that has been modified by reaction of at least a portion of the hydroxyl groups on the saccharide repeat units with a compound to form an ester-linked or an ether-linked substituent. For example, the cellulosic ethyl cellulose has an ether linked ethyl substituent attached to the saccharide repeat unit, while the cellulosic cellulose acetate has an ester linked acetate substituent.

A preferred class of cellulosics for the erodible matrix comprises aqueous-soluble and aqueous-erodible cellulosics such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC). A

particularly preferred class of such cellulosics comprises various grades of low viscosity (MW less than or equal to 50,000 daltons) and high viscosity (MW greater than 50,000 daltons) HPMC. Commercially available low viscosity HPMC polymers include the Dow METHOCEL series E5, E15LV, E50LV and K100LY, while high viscosity HPMC polymers include E4MCR, E10MCR, K4M, K15M and K100M; especially preferred in this group are the METHOCEL K series. Other commercially available types of HPMC include the Shin Etsu METOLOSE 90SH series.

Although the primary role of the erodible matrix material is to control the rate of release of the active agent in solubility-improved form to the environment of use, the inventors have found that the choice of matrix material can have a large effect on the maximum drug concentration attained by the device as well as the maintenance of a high drug concentration. In one embodiment, the matrix material is a concentration-enhancing polymer, as defined herein below.

Other materials useful as the erodible matrix material include, but are not limited to, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, N.J.) and other acrylic acid derivatives such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl) methacrylate chloride.

The erodible matrix polymer may contain a wide variety of the same types of additives and excipients known in the pharmaceutical arts, including osmopolymers, osmagens, solubility-enhancing or -retarding agents and excipients that promote stability or processing of the device.

The formulation may comprise an excipient that is a swellable material such as a hydrogel in amounts that can swell and expand. Examples of swellable materials include polyethylene oxide, hydrophilic polymers that are lightly cross-linked, such cross-links being formed by covalent or ionic bond, which interact with water and aqueous biological fluids and swell or expand to some equilibrium state. Swellable materials such as hydrogels exhibit the ability to swell in water and retain a significant fraction of water within its structure, and when cross-linked they will not dissolve in the water. Swellable polymers can swell or expand to a very high degree, exhibiting a 2 to 50 fold volume increase. Specific examples of hydrophilic polymeric materials include poly(hydroxyalkyl methacrylate), poly(N-vinyl-2-pyrrolidone), anionic and cationic hydrogels, polyelectrolyte complexes, poly(vinyl alcohol) having a low acetate residual and cross-linked with glyoxal, formaldehyde, or glutaraldehyde, methyl cellulose cross-linked with dialdehyde, a mixture of cross-linked agar and carboxymethyl cellulose, a water insoluble, water-swellable copolymer produced by forming a dispersion of finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, butylene, or isobutylene cross-linked with from 0.001 to about 0.5 moles of a polyunsaturated cross-linking agent per mole of maleic anhydride in the copolymer, water-swellable polymers of N-vinyl lactams, cross-linked polyethylene oxides, and the like. Other examples of swellable materials include hydrogels exhibiting a cross-linking of 0.05 to 60%, hydrophilic hydrogels known as Carbopol acidic carboxy polymer, Cyanamer™ polyacrylamides, cross-linked water-swellable indene-maleic anhydride polymers, Good-Rite™ polyacrylic acid, starch graft copolymers, Aqua-Keeps.™ acrylate polymer, diester cross-linked polyglucan, and the like.

The formulations may comprise additives such as polyethylene oxide polymers, polyethylene glycol polymers, cellulose ether polymers, cellulose ester polymers, homo- and copolymers of acrylic acid cross-linked with a polyalkenyl polyether, poly(meth)acrylates, homopolyers (e.g., polymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythritol), copolymers (e.g., polymers of acrylic acid and C_{10}-C_{30} alkyl acrylate crosslinked with allyl pentaerythritol), interpolymers (e.g., a homopolymer or copolymer that contains a block copolymer of polyethylene glycol and a long chain alkyl acid ester), disintegrants, ion exchange resins, polymers reactive to intestinal bacterial flora (e.g., polysaccharides such as guar gum, inulin obtained from plant or chitosan and chondrotin sulphate obtained from animals or alginates from algae or dextran from microbial origin) and pharmaceutical resins.

Polyalkylene Oxides

The pharmaceutical composition of the invention may comprise at least one polyalkylene oxide having an average molecular weight of no more than about 300,000 may be a polyethylene oxide, a polymethylene oxide, a polypropylene oxide, or a copolymer thereof. In exemplary embodiments, the first polyalkylene oxide is a polyethylene oxide. In some embodiments, the polyalkylene oxide, which may be polyethylene oxide, has an average molecular weight of about 300,000. In other embodiments, the polyalkylene oxide, which may be polyethylene oxide, has an average molecular weight of about 200,000. In specific embodiments, the polyalkylene oxide, which may be polyethylene oxide, has an average molecular weight of about 100,000.

In exemplary embodiments, the pharmaceutical composition of the invention may comprise polyalkylene oxide having an average molecular weight of at least 1,000,000 may be a polyethylene oxide, a polymethylene oxide, a polypropylene oxide, or a copolymer thereof. In exemplary embodiments, the polyalkylene oxide is a polyethylene oxide. In some embodiments, the second polyalkylene oxide, which may be polyethylene oxide, has an average molecular weight of about 2,000,000. In other embodiments, the polyalkylene oxide, which may be polyethylene oxide, has an average molecular weight of about 4,000,000. In further embodiments, the second polyalkylene oxide, which may be polyethylene oxide, has an average molecular weight of about 5,000,000. In still other embodiments, the polyalkylene oxide, which may be polyethylene oxide, has an average molecular weight of about 7,000,000. In additional embodiments, the polyalkylene oxide, which may be polyethylene oxide, has an average molecular weight of about 8000,000. In other embodiments, the polyalkylene oxide, which may be polyethylene oxide, has an average molecular weight of about 15,000,000.

In exemplary embodiments, the polymer may be selected from the group comprising polyalkylene oxides, preferably polymethylene oxide, polyethylene oxide, polypropylene oxide; polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers thereof, and mixtures of at least two of the stated polymers.

In exemplary embodiments, the polymer may be a water-soluble polymer for use either as a base polymer material or as a dissolution modifying agent such as polyethylene oxide (PEO), for example the brand name POLYOX® (Dow). It is recognized that the thermoplastic polymers may be used in varying molecular weights, such as 100K, 200K, 300K, 400K, 600K, 900K, 1000K, 2000K, 4000K, 5000K, 7000K and 8000K, and optionally combinations thereof. In a pre-

ferred embodiment, the PEO is a high molecular weight PEO. In a preferred embodiment, the PEO has a molecular weight of about 7,000,000. In a preferred embodiment, the PEO has a molecular weight between about 4,000,000 and 8,000,000. Examples of polyethylene oxide include POLYOX water soluble resin, which is listed in the NF and has approximate molecular weights which range from 100,000 to about 8,000,000. A preferred polyethylene oxide is POLYOX WSR-80, POLYOX WSR N-750, POLYOX WSR-205, POLYOX WSR-1105, POLYOX WSR N-12K, POLYOX WSR N-60K, WSR-301, WSR Coagulant, WSR-303, and combinations thereof.

The amount of polyalkylene oxide present in the pharmaceutical composition can and will vary and in general, the amount of the polyalkylene oxide present in the pharmaceutical composition may range from about 10% to about 95% by weight of the composition. In various embodiments, the amount of the polyalkylene oxide present in the pharmaceutical composition may range from about 20% to about 90%, from about 30% to about 80%, or from about 35% to about 70% by weight of the pharmaceutical composition. In various embodiments, the amount of the polyalkylene oxide present in the pharmaceutical composition may be about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

In the above described embodiments high molecular weight polyethylene oxide having, based on rheological measurements, an approximate molecular weight of from 2,000,000 to 15,000,000 or from 2,000,000 to 8,000,000 may be used. In particular polyethylene oxides having, based on rheological measurements, an approximate molecular weight of 2,000,000, 4,000,000, 7,000,000 or 8,000,000 may be used. In particular polyethylene oxides having, based on rheological measurements, an approximate molecular weight of 4,000,000, may be used.

In embodiments wherein the composition further comprises at least one low molecular weight polyethylene oxide is used polyethylene oxides having, based on rheological measurements, an approximate molecular weight of less than 1,000,000, such as polyethylene oxides having, based on rheological measurements, an approximate molecular weight of from 100,000 to 900,000 may be used. The addition of such low molecular weight polyethylene oxides may be used to specifically tailor the release rate such as enhance the release rate of a formulation that otherwise provides a release rate to slow for the specific purpose. In such embodiments at least one polyethylene oxide having, based on rheological measurements, an approximate molecular weight of 100,000 may be used.

In certain such embodiments the composition comprises at least one polyethylene oxide having, based on rheological measurements, an approximate molecular weight of at least 1,000,000 and at least one polyethylene oxide having, based on rheological measurements, an approximate molecular weight of less than 1,000,000, wherein the composition comprises at least about 10% (by wt) or at least about 20% (by wt) of the polyethylene oxide having, based on rheological measurements, an approximate molecular weight of less than 1,000,000. In certain such embodiments the curing temperature is less than about 80° C. or even less than about 77° C. In certain embodiments the overall content of polyethylene oxide in the composition is at least about 80% (by wt).

Lubricant

In exemplary embodiments, the pharmaceutical composition of the invention may include lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof and other tableting aids such a magnesium stearate and microcrystalline cellulose

The pharmaceutical compositions disclosed herein may also further comprise at least one lubricant, which facilitates preparation of solid dosage forms of the pharmaceutical composition. Non-limiting examples of suitable lubricants include magnesium stearate, calcium stearate, zinc stearate, colloidal silicon dioxide, hydrogenated vegetable oils, sterotex, polyoxyethylene monostearate, polyethylene glycol, sodium stearyl fumarate, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, and light mineral oil. In exemplary embodiments, the lubricant may be magnesium stearate.

In embodiments in which the lubricant is included in the pharmaceutical composition, the amount of the lubricant may range from about 0.1% to about 3% by weight of the pharmaceutical composition. In various embodiments, the amount of the lubricant may range from about 0.1% to about 0.3%, from about 0.3% to about 1%, or from about 1% to about 3% by weight of the pharmaceutical composition. In exemplary embodiments, the amount of the lubricant may be about 1% by weight of the pharmaceutical composition.

Coating

The pharmaceutical composition can be coated with one or more enteric coatings, seal coatings, film coatings, barrier coatings, compress coatings, fast disintegrating coatings, or enzyme degradable coatings.

In some cases, the formulation disclosed herein is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is a form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of drug actives. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating material is clear. Exemplary coating materials include, without limitation, polyvinyl alcohol (PVA), cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), methacrylic acid copolymers, cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose (HPMC), hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate), shellac, sodium alginate, and zein. In some embodiments, the coating material comprises or is PVA. In some embodiments, the coating material comprises or is HPMC. An exemplary PVA-based coating material includes Opadry II. In some instances, the coating material is about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% of the weight of the formulation. In some instances, the coating material represent between about 1% and about 15% of the total weight of each first particulate, including, but not limited to, between about 5% and about 10%, between about 6% and about 10%, between about 7% and about 10%, between about 8% and about 10%, or between about 9% and about 10%. In some instances, the coating material is greater than about 2%, greater than about 3%, greater than about 4%, greater than about 5%, greater than about 6%, greater than about 7%, greater than about

8%, greater than about 9%, or greater than about 10% of the weight of the formulation. In some instances, the coating material is less than about 2%, less than about 3%, less than about 4%, less than about 5%, less than about 6%, less than about 7%, less than about 8%, less than about 9%, or less than about 10% of the weight of the formulation.

Multiple coatings can be applied for desired performance. Further, the dosage form can be designed for immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, synchronized release, or targeted delayed release. For release/absorption control, solid carriers can be made of various component types and levels or thicknesses of coats, with or without an active ingredient. Such diverse solid carriers can be blended in a dosage form to achieve a desired performance. The definitions of these terms are known to those skilled in the art. In addition, the dosage form release profile can be affected by a polymeric matrix composition, a coated matrix composition, a multiparticulate composition, a coated multiparticulate composition, an ion-exchange resin-based composition, an osmosis-based composition, or a biodegradable polymeric composition. Without wishing to be bound by theory, it is believed that the release may be effected through favorable diffusion, dissolution, erosion, ion-exchange, osmosis or combinations thereof.

Dosage forms of the invention can further be coated with, for example, a seal coating, an enteric coating, an extended release coating, or a targeted delayed release coating. These various coatings are known in the art, but for clarity, the following brief descriptions are provided: seal coating, or coating with isolation layers: Thin layers of up to 20 microns in thickness can be applied for variety of reasons, including for particle porosity reduction, to reduce dust, for chemical protection, to mask taste, to reduce odor, to minimize gastrointestinal irritation, etc. The isolating effect is proportional to the thickness of the coating. Water soluble cellulose ethers are preferred for this application. HPMC and ethyl cellulose in combination, or Eudragit E100, may be particularly suitable. In exemplary embodiments, the coating may be OPADRY® Y-1-7000, a coating ready mix from Colorcon. Opadry Y-1-7000 contains hypromellose 5 cP, titanium dioxide and macrogol/PEG 400. Traditional enteric coating materials listed elsewhere can also be applied to form an isolating layer.

Optionally, the sustained-release matrix multiparticulate systems, tablets, or capsules can be coated with a sustained release coating such as the sustained release coatings described herein. Such coatings preferably include a sufficient amount of hydrophobic and/or hydrophilic sustained-release material to obtain a weight gain level from about 2 to about 25 percent, although the overcoat may be greater depending upon, e.g., the desired release rate. In certain embodiments, a sustained release coating is applied to the sustained release spheroids, granules, or matrix multiparticulates. In such embodiments, the sustained-release coating may include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein. The coating is preferably derived from an aqueous dispersion of the hydrophobic sustained release material.

In other preferred embodiments of the present invention, the sustained release material comprising the sustained-release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly (methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Rohm GMBH and Co. Kg Darmstadt, Germany. There are several different types of Eudragit®. For example, Eudragit E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit RL and Eudragit RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent; however, dosage forms coated with Eudragit RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Methyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Extended release coatings are designed to effect delivery over an extended period of time. The extended release coating is a pH-independent coating formed of, for example, ethyl cellulose, hydroxypropyl cellulose, methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, acrylic esters, or sodium carboxymethyl cellulose. Various extended release dosage forms can be readily designed by one skilled in art to achieve delivery to both the small and large intestines, to only the small intestine, or to only the large intestine, depending upon the choice of coating materials and/or coating thickness.

Enteric coatings are mixtures of pharmaceutically acceptable excipients which are applied to, combined with, mixed with or otherwise added to the carrier or composition. The coating may be applied to a compressed or molded or extruded tablet, a gelatin capsule, and/or pellets, beads, granules or particles of the carrier or composition. The coating may be applied through an aqueous dispersion or after dissolving in appropriate solvent.

In certain embodiments, the pharmaceutical composition, upon oral administration to a human or non-human patient in need thereof, provides controlled release for at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 24, 36, 48, 72, 96, 120, 144, or 168 hours.

The term "sustained release" refers release of a drug from its dosage form (e.g., tablet) at such a rate that its blood levels are maintained within the therapeutic range (i.e., at or above minimum effective concentration (MEC)) but below toxic levels over an extended period of time (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24, 36, 48, 72, 96, 120, 144, or 168 hours or greater). The term "sustained release" may be used interchangeably with "slow-release," "controlled release," or "extended release." The sustained release property of a dosage form is typically measured by an in vitro dissolution method and confirmed by an in vivo blood concentration-time profile (i.e., a pharmacokinetic profile).

In certain embodiments, the pharmaceutical compositions of the present invention release about 90% to 100% of their pharmaceutically active agents in a linear or near linear fashion for at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 36, 48, 72, 96, 120, 144, or 168 hours in an in vitro dissolution analysis.

Delayed release generally refers to the delivery so that the release can be accomplished at some generally predictable location in the lower intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. The preferred method for delay of release is coating. Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery to the lower gastrointestinal tract. Polymers for use in the present invention are anionic carboxylic polymers.

In exemplary embodiments, the coating may comprise shellac, also called purified lac, a refined product obtained from the, resinous secretion of an insect. This coating dissolves in media of pH>7.

Colorants, detackifiers, surfactants, antifoaming agents, lubricants, stabilizers such as hydroxy propyl cellulose, acid/base may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

Hardness

In certain embodiments, the present invention is directed to a solid oral extended release pharmaceutical dosage form comprising an extended release matrix formulation, the extended release matrix formulation comprising

a composition comprising:

(1) at least one polyethylene oxide having, based on rheological measurements, an approximate molecular weight selected from the group consisting of at least about 1,000,000; at least about 2,000,000; at least about 3,000,000; at least about 4,000,000; at least about 5,000,000; at least about 6,000,000; at least about 7,000,000; and at least about 8,000,000; and

(2) at least one active agent; and

wherein the extended release matrix formulation when subjected to an indentation test has a "hardness" of at least about 200 N.

In certain such embodiments of the invention the extended release matrix formulation has a hardness or cracking force of at least about 110 N, preferably of at least about 120 N, at least about 130 N or at least about 140 N, more preferably of at least about 150 N, at least about 160 N or at least about 170 N, most preferably of at least about 180 N, at least about 190 N, at least about 200 N, at least about 210 N, at least about 220 N, at least about 230 N, at least about 240 N, or at least about 250 N.

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

EXAMPLES

Example 1

Ketamine Sustained-release Tablets 60 mg Formulation

Excipients	mg/tablet	% (w/w)
Ketamine HCl	69.20	16.80
Polyethylene Oxide	326.80	79.32
Magnesium Stearate	4.00	0.97
Opadry White Y-1-7000 (Coating)	12.00	2.91
Total	412.00	100.00

Manufacturing Steps:

1. Mix ketamine HCl with polyethylene oxide in a suitable mixer until uniformed.
2. Blend magnesium stearate into the above dry powder mixture.
3. Compress the final powder blend into tablets with aim tablet mass of 400 mg and aim tablet hardness of 210 N.
4. Perform initial coating to protect tablets from damage in next step of tablets curing.
5. Cure tablets at the temperature range of 70° C. to 75° C. to achieve desired firmness.
6. Continue to coat tablets from above step to gain sufficient weight.

Example 2

Study ZPS-603 (Study 603) was a hybrid study design with 4 cohorts and multiple study objectives. The objectives of Cohorts 1, 2 and 3 were to evaluate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of an extended release ketamine oral formulation in healthy volunteers after single dose and multiple doses. The design was a double-blind, placebo-controlled single and multiple ascending dose study in healthy volunteers. Doses were 60 mg, 120 mg and 240 mg for Cohorts 1, 2 and 3 respectively. Each dose level was initially given as a single dose, then one week later as 5 doses given at 12 hour intervals. Endpoints included safety, tolerability, ketamine and norketamine PK, and PD (suicidality assessments, and dissociative symptom rating scale scores).

The objective of Cohort 4 was to evaluate efficacy, safety, PK and PD of an extended release ketamine oral formulation in patients with treatment-resistant depression and/or treatment-resistant anxiety (TRD/TRA). Patients were selected based on prior demonstrated mood response to subcutaneous ketamine, and clinically significant scores on the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery 1979) and/or the Hamilton Anxiety Scale (HAMA; Hamilton 1959). The design was an open label multiple ascending dose study. The initial dose was 60 mg, and could be escalated by an additional 60 mg 12 hourly, based on assessment of mood symptoms, to a maximum dose of 240 mg, with a total of 7 doses given 12 hourly between 0 and 72 hours. Endpoints included safety, tolerability, ketamine and norketamine PK, and PD (mood ratings including the Fear Questionnaire (FQ; Marks 1979), HAMA and MADRS, and dissociative symptom rating scale scores).

A protocol amendment added a further objective to Cohort 4, namely to evaluate the safety and efficacy of up to 3 months dosing of the extended release ketamine oral formulation in patients with TRD/TRA, who responded to treatment in the initial 96 hour ascending dose phase of ZPS-603, in an open-label extension (OLE) treatment phase. Endpoints for the OLE were similar to those of the initial 96 hour ascending dose phase of ZPS-603.

Results, Cohorts 1-3:

Demographics: Mean (SD) parameters for Cohort 1-3 participants are shown in Table 1. One subject in Cohort 2 (#16) withdrew from the study between single and multiple dosing, for reasons unrelated to safety/tolerability.

TABLE 1

Demographic parameter			
	Cohort 1	Cohort 2	Cohort 3
Ketamine dose	60 mg	120 mg	240 mg
N ketamine/placebo	6/2	6/2	6/2
Dropouts	0	1	0
Age (years)	27 ± 10	23 ± 3	21 ± 1
Number of Males/Females	6/2	7/1	5/3
Weight (kg)	83.8 ± 10.2	74.9 ± 9.7	68.9 ± 6.7
Height (cm)	1.80 ± 0.09	1.76 ± 0.07	1.73 ± 0.07
BMI (kg/m^2)	25.9 ± 1.5	24.2 ± 2.1	23.1 ± 1.3

Safety: There were no changes of clinical significance in vital signs, ECGs, safety laboratory tests or urinalyses in any subjects in Cohorts 1-3 during or after study completion.

Tolerability: Adverse events reported by study group are shown in Table 2. The only adverse event to show dose-related increases in frequency was dissociation, in subjects dosed with 240 mg.

Adverse event	Cohort 1 (60 mg)	Cohort 2 (120 mg)	Cohort 3 (240 mg)	All cohorts (Placebo)
Vascular disorders				
Syncope	0	0	0	1
Dizziness	0	1	1	0
Respiratory, thoracic and mediastinal disorders				
Throat irritation	1	0	0	0
epistaxis	1	0	0	0
Psychiatric disorders				
Restlessness	1	0	0	0
Dissociation	0	0	11	2
Nervous system disorders				
Headache	2	0	1	0
Gastrointestinal disorders				
Nausea	0	0	1	0
General disorders and administration site conditions				
Swelling at catheter site	0	0	0	1
Total	5	1	14	4

Pharmacodynamics:

CADSS: Mean CADSS scores over time are shown in FIG. **2**. Minor increases were noted at 3 hours after single dosing in Cohorts 1 and 3 (FIG. **2**A), and at 3-12 hours after the first dose in the multiple dose phase for Cohort 3 (FIG. **2**B). (It should be noted that the maximum score on this scale is 84 points and that these are minimal changes compared with subcutaneous or IV ketamine dosing).

Suicidality Ratings: No participants reported suicidal ideation at any time in Cohorts 1-3, as assessed by the Columbia Suicide Severity Rating Scale.

Pharmacokinetics: FIG. **3** shows mean concentration-time profiles of ketamine and norketamine after single and multiple doses of 60, 120 and 240 mg. Concentrations of both analytes were relatively stable for 5-10 hours after dosing, consistent with the sustained release characteristics of the tablet. Norketamine concentrations were approximately 10-fold higher than ketamine concentrations in both plots, reflecting extensive first pass metabolism after oral dosing. For all 3 cohorts, ketamine and norketamine pharmacokinetic parameters appeared to follow first order kinetics, specifically AUC and Cmax were dose proportional after single and multiple doses of ketamine 60 mg, 120 mg and 240 mg extended release tablets (FIG. **4**). There appeared to be evidence of autoinduction, in that the multiple dose AUC_{0-12} values for both ketamine and norketamine were less than the single dose AUC 0-∞, and the ratio of these decreased in a dose-related manner (see Table 3). The mechanism for induction appears to be via CYP2B6. Ketamine per induces activity of CYP2B6 (Chen 2010), and is itself metabolized by this enzyme.

TABLE 3

Ketamine						
	AUC			Cmax		
Dose	SD[1] (0-∞)	MD[2] (0-12)	Ratio[3]	SD[1]	MD[2] (0-12)	Ratio[3]
60 mg	79.24	74.18	**0.94**	9.71	11.91	1.23
120 mg	196.92	133.11	**0.68**	16.40	20.66	1.26
240 mg	384.58	217.41	**0.57**	37.98	41.57	1.09

TABLE 4

Single and multiple dose AUC and Cmax for ketamine (upper panel) and norketamine (lower panel), and ratios. MD/SD AUC ratios less than 1 are suggestive of autoinduction (bolded).

Norketamine

	AUC			Cmax		
Dose	SD[1] (0-∞)	MD[2] (0-12)	Ratio[3]	SD[1]	MD[2] (0-12)	Ratio[3]
60 mg	872.21	980.54	1.12	73.74	124.65	1.69
120 mg	2133.09	1697.06	**0.80**	161.24	229.91	1.43
240 mg	4079.19	3019.81	**0.74**	314.67	421.11	1.34

Results, Cohort 4:

Demographics: Mean (SD) parameters for Cohort 4 participants are shown in Table 5.

TABLE 5

Demographic parameter

	Cohort 1
Dropouts	0
Age (years)	27 ± 4
Number of Males/Females	4/3
Weight (kg)	82.1 ± 22.3
Height (cm)	1.75 ± 0.07
BMI (kg/m^2)	26.5 ± 5.6

Diagnoses: All 7 patients had current diagnoses of Social Anxiety Disorder. Five also had diagnoses of Major Depressive Disorder (MDD), and one had comorbid Generalized Anxiety Disorder. At screening, mean HAMA score was 22.9 (consistent with moderate severity) and mean FQ score was 48.4 (approximately 2-fold higher than the non-clinical population mean). Mean MADRS score in the 5 patients with MDD was 31.2 (consistent with moderate depression).

Dosing: On Day 1 all 7 patients were dosed with 1×60 mg tablets in the morning. All 7 patients received 2×60 mg tablets at 12 hours, and all 7 patients received 3×60 mg tablets at 24 hours. At 36 hours 2 patients received 3×60 mg tablets and 5 patients received 4×60 mg tablets. At 48 hours, 1 patient received 3×60 mg tablets and 6 patients received 4×60 mg tablets. At 56 and 72 hours all 7 patients received 4×60 mg tablets (see Table 6).

TABLE 6

	Day 1 (mg)		Day 2 (mg)		Day 3 (mg)		Day 4 (mg)
Patient ID	am	pm	am	pm	am	pm	am
039-25	60	120	180	180	180	240	240
042-26	60	120	180	240	240	240	240
040-27	60	120	180	240	240	240	240
043-28	60	120	180	240	240	240	240
041-29	60	120	180	180	240	240	240
038-30	60	120	180	240	240	240	240
044-32	60	120	180	240	240	240	240

Safety: There were no changes of clinical significance in vital signs, ECGs, safety laboratory tests or urinalyses in any subjects in Cohort 4 during or after study completion.

Tolerability: Adverse events reported by Cohort 4 are shown in Table 7. Overall, single and multiple doses of the extended release ketamine tablets were well tolerated.

TABLE 7

Adverse Events (total no. AEs reported/subject n)

	Cohort 4
Feeling spaced out	1/1
Headache	3/3
Lightheadedness	1/1

Pharmacodynamics:

CADSS: Mean CADSS scores over time are shown in FIG. **5**A. Mean CADSS scores tended to decrease over time. This contrasts markedly from the change in CADSS scores after subcutaneous (SC) ketamine. FIG. **5**B shows mean CADSS scores up to 3 hours after oral and SC dosing, in six of seven Cohort 4 participants with both sets of data. Overall, multiple dose oral ketamine was not associated with dissociative symptoms, as evaluated by the CADSS scale.

Anxiety Rating Scales: HAMA and FQ: Individual and group mean HAMA and FQ scores by timepoint are shown in FIG. **6** (6A: HAMA; 6B: FQ) There was a consistent trend for both scores to decrease over time, most noticeably in patients with higher baseline scores. The trend for gradual improvement in anxiety contrasts markedly from the rapid reduction in anxiety scores after subcutaneous (SC) ketamine. FIG. **7** shows mean HAMA scores after oral and SC dosing, in six of seven Cohort 4 participants with both sets of data. All seven participants were assessed to be treatment responders (>50% reduction) based on changes in HAMA scores, and six of seven participants were responders based on changes in FQ scores.

MADRS: Individual and group mean MADRS scores by timepoint are shown in FIG. **8**. There was a consistent trend for scores to decrease over time, most noticeably in patients with higher baseline scores. All seven participants were assessed to be treatment responders (>50% reduction) based on change in MADRS scores. Subject 042-026 reported worsening symptoms of depression at 48 and 72h, without changes in ratings of anxiety. After discussion with clinic staff he reported that these were related to feelings of sadness at his experience of being excluded from group activities, rather than substantial and persistent changes in mood suggestive of a relapse of major depression. Following this discussion his MADRS scores fell again.

FIG. **9** shows smoothed mean depression (MADRS; **9**A) and anxiety (FQ, HAMA; **9**B and C) scores in 3 patients in Cohort 4, who entered a subsequent 3 month open-label extension (OLE) phase. All three patients reported improvements in mood ratings during this time. Mean depression ratings appeared to take 6 weeks for maximal improvement (FIG. **9**A), whereas mean maximal anxiety scale improvement appeared to occur by week **2** (FIGS. **9**B, **9**C).

Pharmacokinetics: FIG. **10** shows mean concentration-time profiles of ketamine and norketamine over 96 hours in Cohort 4. Dose-related increases in both ketamine and norketamine plasma concentrations were noted out to 48h, as patients continued to take higher doses. Norketamine concentrations were consistently higher than ketamine concentrations at all time points, reflecting extensive first pass metabolism. The data indicate a large inter-subject and intra-subject variation in the PK profiles.

To assess the impact of repeated dosing on enzyme induction, individual ketamine:norketamine (K:NK) ratios were calculated for each time point. These are plotted in FIG. **11**. The mean ratio of K:NK was approximately 11 at 0 h, and progressively decreased to approximately 5 at 96h. The correlation of K:NK ratios against time gave a coefficient of

determination (r^2) of 0.26. Data variability (expressed as % coefficient of variation) also decreased during multiple dosing, from 44% at 0 h to 23% at 96h. These data are suggestive of increased first pass metabolism associated with repeat 12-hourly dosing, which appears to asymptote by 72 hours.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

What is claimed is:

1. A solid, oral, extended release pharmaceutical tablet comprising:

(A) a core comprising:

i) a therapeutically effective amount of an active agent selected from the group consisting of ketamine, pharmaceutically acceptable salts thereof, and combinations thereof, wherein the active agent is present at a concentration of at least about 12% ketamine base w/w of the core;

ii) at least one high molecular weight polyethylene oxide (PEO) that is cured, wherein said high molecular weight PEO has an approximate molecular weight of about 7 million, based upon rheological measurements, and is present in an amount of at least 75% (by weight) of the core; and

iii) magnesium stearate is present at a concentration of about 1% to about 3% by weight;

(B) a coating on said core, wherein said tablet

is crush resistant and has a breaking strength of at least about 200 N; and wherein said tablet provides a pharmacokinetic parameter selected from the group consisting of: a mean ketamine Cmax of about 10 ng/mL after administration of a single dose of 60 mg to a patient; a mean ketamine Cmax of about 16 ng/mL after administration of a single dose of 120 mg to a patient; a mean ketamine Cmax of about 38 ng/mL after administration of a single dose of 240 mg;

a mean ketamine $AUC_{0-\infty}$ of about 79 ng·h/mL after administration of a single dose of 60 mg; a mean ketamine $AUC_{0-\infty}$ of about 197 ng·h/mL after administration of a single dose of 120 mg to a patient; a mean ketamine $AUC_{0-\infty}$ of about 385 ng·h/mL after administration of a single dose of 240 mg.

2. The tablet of claim **1** wherein the dosage amount of active agent is selected from the group consisting of about 30 mg, about 60 mg, about 120 mg, and about 240 mg.

3. The tablet of claim **1** wherein the tablet is cured at a temperature of about 70° C. to about 75° C.

4. The tablet of claim **1** wherein the coating comprises:

i) hydroxypropylmethylcellulose;

ii) titanium dioxide; and

iii) polyethylene glycol.

5. The tablet of claim **1** wherein the tablet is suitable for once daily administration or twice-daily administration to a subject.

6. The tablet of claim **1** wherein the tablet has no or minimal dissociative side effects upon administration to a patient.

7. A solid, oral, extended release pharmaceutical tablet comprising:

(A) a core comprising:

i) a therapeutically effective amount of an active agent selected from the group consisting of ketamine, pharmaceutically acceptable salts thereof, and combinations thereof, wherein the active agent is present at a concentration of at least about 12% ketamine base w/w of the core;

ii) at least one high molecular weight polyethylene oxide (PEO) that is cured, wherein said high molecular weight PEO has an approximate molecular weight of about 7 million, based upon rheological measurements, and is present in an amount of at least 75% (by weight) of the core; and

iii) magnesium stearate is present at a concentration of about 1% to about 3% by weight;

(B) a coating on said core, wherein said tablet is crush resistant and has a breaking strength of at least about 200 N; and

wherein said tablet provides a pharmacokinetic parameter selected from the group consisting of: a mean ketamine Cmax of about 12 ng/mL after administration of 5 doses of 60 mg administered every 12 hours to a patient; a mean ketamine Cmax of about 21 ng/mL after administration of 5 doses of 120 mg administered every 12 hours to a patient; a mean ketamine Cmax of about 42 ng/mL after administration of 5 doses of 240 mg administered every 12 hours to a patient;

a mean ketamine AUC_{0-12} of about 74 ng·h/mL after administration of 5 doses of 60 mg administered every 12 hours to a patient; a mean ketamine AUC_{0-12} of about 133 ng·h/mL after administration of 5 doses of 120 mg administered every 12 hours to a patient; a mean ketamine AUC_{0-12} of about 217 ng·h/mL after administration of 5 doses of 240 mg administered every 12 hours to a patient.

8. The tablet of claim **7** wherein the tablet is cured at a temperature of about 70° C. to about 75° C.

9. The tablet of claim **7** wherein the coating comprises:

i) hydroxypropylmethylcellulose;

ii) titanium dioxide; and

iii) polyethylene glycol.

10. The tablet of claim **7** wherein the tablet is suitable for once daily administration or twice-daily administration to a subject.

11. The tablet of claim **7** wherein the tablet has no or minimal dissociative side effects upon administration to a patient.

* * * * *